Rate Control in Atrial Fibrillation

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.[1] Currently, the prevalence is 5.5% in the Netherlands, increasing with age to almost 20%.[2] Due to the aging population the prevalence will increase even more. It is currently estimated that the prevalence will double over the next 30-50 years.[1-3] AF is associated with increased cardiovascular mortality and morbidity. The death rate is doubled in patients with AF.[4-6] Stroke is one of the major complications of the arrhythmia, and in about 20% of patients stroke is the first presentation of AF.[7] Strokes associated with AF have a worse prognosis.[8,9] In addition, AF can cause or deteriorate heart failure, and AF is independently associated with a worse prognosis in retrospective analyses of patients with heart failure.[10-16] Patients with AF also have an increased bleeding risk due to the use of oral anticoagulation. In addition, the number of hospitalizations for AF increases, especially in the elderly.[17,18] This, in turn, increases the burden of AF on the health care system.[19] Furthermore, AF reduces exercise capacity and quality of life.[20-24] Hence, AF is not a benign disease.

The first published observation of AF was by Bouilland in 1835. He described it as an irregular rhythm and unequal force of the heartbeat.[25] Nothnagel gave it the term 'delirium cordis', due to the irregular arterial pulse.[26] In 1908 the first electrocardiogram of AF was published.[27] Treatment options at that time were limited. To reduce the ventricular rate digoxin was given; the reduction of ventricular rate due to digoxin was already discovered by William Withering in 1785.[28] Furthermore, quinidine could be used to convert AF to sinus rhythm.[29,30] It was not until the 1960's that the electrical cardioversion was introduced by Bernard Lown.[31] Despite this new method which converted AF to sinus rhythm in a high percentage of patients, AF remained a progressive arrhythmia,[31-33] since the success of rhythm control, i.e. long term maintenance of sinus rhythm, was and is limited.[34-38] Moreover, the adverse effects of rhythm control drugs are substantial. Nevertheless, assuming that sinus rhythm would improve prognosis, for years the initial goal was prevention of recurrent AF, i.e. rhythm control. AF was accepted only when rhythm control failed. It was not until the beginning of this decade that it became apparent that there was no difference in outcome between rate and rhythm control.[39-43] The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[40] and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE)[41] were the first two studies which elucidated a comparable prognosis during rate and rhythm control (Table 1). In AFFIRM and RACE together more than 4500 patients were randomized to either rate or rhythm control. The primary outcome of AFFIRM, all cause mortality, did not differ between rate and rhythm control. The primary outcome of RACE, a composite of cardiovascular morbidity and mortality, was also similar between rate and rhythm control. The Pharmacological Intervention in Atrial Fibrillation (PIAF) showed that there was no difference in AF related symptoms between rate and rhythm control.[39] After the first two landmark studies investigating cardiovascular morbidity and mortality, the Strategies of Treatment of Atrial Fibrillation (STAF)[42], the How to Treat Chronic Atrial Fibrillation (HOT CAFE)[43], and the Japanese Rhythm Management Trial for Atrial Fibrillation (J-Rhythm)[44] studies confirmed the equality between rate and rhythm control.

Table 1. Heart rate criteria in the rate versus rhythm control trials

	Primary outcome	Heart rate criteria
AFFIRM[40]	All-cause mortality	≤80 beats/min, and ≤110 beats/min during moderate exercise. On Holter mean heart rate ≤100 beats/min, and not >110% of the maximum predicted heart rate
RACE[41]	Composite endpoint*	<100 beats/min
PIAF[39]	Symptoms related to atrial fibrillation	Diltiazem 90mg, 2-3 times per day, additional rate control therapy at discretion of physician
STAF[42]	Composite endpoint†	-
HOT CAFE[43]	Composite endpoint‡	70-90 beats/min, <140 beats/min during moderate exercise
AF-CHF[45]	Cardiovascular death	≤80 beats/min, and ≤110 beats/ min during 6-min walk test
J Rhythm[44]	Composite endpoint#	60-80 beats/min

* Cardiovascular death, hospitalization for heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe adverse effects or antiarrhythmic drugs
† All cause mortality, stroke or transient ischemic attack, systemic embolism, and cardiopulmonary resuscitation
‡ All cause mortality, thromboembolic complications and intracranial or other major hemorrhage
\# All cause mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, physical/ psychological disability requiring alteration of assigned strategy

The absence of a benefit of rhythm control is caused by the inefficacy and also by the adverse effects of antiarrhythmic drugs. At the time the abovementioned studies were performed, pulmonary vein isolation (PVI) was not yet a widespread method to treat patients with especially paroxysmal AF. It is therefore not clear what the effect of rhythm control, including PVI, on mortality would be. Although PVI is nowadays the cornerstone of rhythm control management in paroxysmal AF patients without severe co-morbidity, success rates are still low in patients with longstanding persistent and permanent AF.[1]

As mentioned, the AFFIRM, RACE, PIAF, STAF, and HOT CAFE, J-Rhythm, and Atrial Fibrillation and Congestive Heart Failure (AF-CHF) studies demonstrated that rate control was comparable to rhythm control regarding prognosis in patients with AF (Table 1).[39-45] From that moment on, rate control became frontline therapy in older patients with few or acceptable symptoms of AF. However, the rate control criteria used in the rate versus rhythm control trials were not homogeneous (Table 1). In addition, the rate control criteria used in previous guidelines were not evidence based.[46] Digoxin was the cornerstone of AF treatment during the largest part of the last century. Although digoxin was used since the 18th century,[47] it only became apparent in the 1970's that treatment with digoxin alone did not decrease the heart rate adequately during exercise.[48,49]

Newer rate control drugs became available much later. Since then, drugs frequently used to institute rate control consist of beta-blockers, nondihydropiridine calcium-channel blockers and, as mentioned, digoxin. From the 70's of the last century until now several studies have been performed evaluating the effect of negative dromotropic drugs (beta-blockers, nondihydropiridine calcium-channel blockers,

digoxin, amiodarone, and dronedarone) on heart rate during AF. At first, the focus was on heart rate during rest and exercise.[50-54] It was expected that exercise capacity would improve due to a reduction in heart rate. However, later studies showed no improvement of exercise capacity with a more physiological rate response during exercise.[55-61] A number of studies assessed hemodynamics and gas exchange during AF. Several negative dromotropic drugs were compared with placebo or comparisons between different negative dromotropic drugs were evaluated. Though these studies also showed a reduction in heart rate during exercise, no improvement of maximal oxygen uptake was observed.[56,57,60,62,63] This is of major importance considering that maximal oxygen uptake is an indicator for left ventricular function.[64]

One of the first studies that evaluated left ventricular function with regard to different rate control strategies was performed by Khand and colleagues.[65] The investigators observed an improvement of left ventricular function in patients treated with carvedilol on top of digoxin. This improvement was not observed in patients treated with placebo and digoxin. There were no differences in 6-minute walking distances or brain natriuretic peptide. A large retrospective analysis of the AFFIRM evaluated the effect of heart rate on prognosis.[66] All patients randomized to rate control who were in AF at baseline and at 2 months follow-up were included in this analysis. There was no difference in cardiovascular hospitalization or death between the quartiles of achieved heart rate at rest at 2 months follow-up. Resting heart rate was not a predictor for all cause mortality or cardiovascular hospitalization.

The AFFIRM and RACE studies used different definitions of adequate rate control. In the AFFIRM the following rate control approach was used: resting heart rate below 80 beats per minute, and a heart rate below 110 beats per minute during a 6-minute walk test or a mean heart rate during 24 hour Holter monitoring below 100 beats per minute and no maximum heart rate above 110% of the maximum predicted heart rate.[67] In the RACE the rate control criterion was a resting heart rate below 100 beats per minute.[41] A pooled analysis of AFFIRM and RACE evaluated differences in outcome between the studies.[68] The mean heart rate was lower in the patients included in the AFFIRM trial. There was no difference in outcome between the patients included in AFFIRM or RACE, though a heart rate >100 beats per minute was associated with a worse outcome.

All available studies on heart rate control during permanent AF were retrospective analyses. These retrospective data indicated that there was no benefit of a strict rate control approach compared with a more lenient rate control approach in terms of cardiovascular morbidity and mortality. Furthermore, strict rate control was difficult to achieve. In the AFFIRM trial a strict rate control approach was used, as mentioned above. To achieve these strict criteria, frequent medication changes and drug combinations were needed. Eventually about two thirds of patients were treated according to the protocol.[69] This indicates that a strict rate control approach is not attainable in all patients with AF.

Quality of life and heart rate are also assumed to be related. A higher heart rate could cause more or more severe symptoms than a lower heart rate. However, instituting a stricter rate control strategy requires more negative dromotropic drugs.

The possible adverse side effects of more and higher dosages of negative dromotropic drugs could reduce the beneficial effect of a lower heart rate. In a sub-analysis of AFFIRM there was no relation between quality of life and achieved resting heart rate at 2 months follow-up.[66] Prospective data on quality of life and heart rate in patients with permanent AF are lacking.

The current data indicate that cardiovascular morbidity, mortality, and quality of life are not influenced by heart rate. However, as mentioned, all available data on ventricular frequency during AF are retrospective. Thus, prospective data on heart rate control in patients with permanent AF should give us better insight in how to treat this specific patient cohort.[70]

Aim of this thesis

Rate control is frontline therapy in patients with AF, especially in those without severe symptoms, or after failure of rhythm control. However, an evidence based strategy concerning the treatment of patients with permanent AF is lacking. The aim of this thesis is to evaluate rate control strategies in patients with permanent AF, in terms of cardiovascular morbidity, mortality, all cause hospitalizations, and quality of life.

In **chapter 2** we describe patients with persistent AF randomized to the rate control arm of the RACE trial. We evaluated cardiovascular morbidity, mortality, echocardiographic parameters, and quality of life.

Previously, no randomized clinical trial was performed evaluating different rate control strategies. Therefore a randomized clinical trial was performed evaluating lenient and strict rate control in terms of cardiovascular morbidity and mortality, i.e. the Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II (RACE II) study. The hypothesis was that there was no difference in outcome between lenient and strict rate control. The results of the RACE II are presented in **chapter 3**.

Strict rate control is a challenging treatment strategy since it is difficult to achieve. The strict rate control approach used in AFFIRM was attained in about two thirds of the patients. Perhaps the assumed equality between lenient and strict rate control strategies regarding outcome is caused by the failure of achieving strict rate control. In **chapter 4** we investigated whether outcome was comparable between patients included in RACE II with successful strict, failed strict, or lenient rate control.

When instituting rate control in a patient with AF, clinicians often use AF-related symptoms as a marker for adequate rate control. The evaluation of quality of life in the RACE II study is therefore of major importance, especially since the study hypothesized that outcome would be comparable between lenient and strict rate control, and future therapy could be guided on symptoms experienced by the patients. In **chapter 5** we present the results of the quality of life analyses in the RACE II.

The most firm outcome parameter assessing different treatment strategies is all-cause mortality. However, the RACE II was not powered to evaluate differences

in all-cause mortality between lenient and strict rate control. An alternative outcome parameter is cardiovascular hospitalization. We therefore performed a post-hoc analysis of RACE II evaluating possible differences between lenient and strict rate control in all-cause mortality and cardiovascular and non-cardiac hospitalizations. These results are presented in **chapter 6**.

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2 Does Intensity of Rate Control Influence Outcome in Persistent Atrial Fibrillation Data of the RACE study

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Abstract

Introduction

Large trials have demonstrated that rate control is an acceptable alternative for rhythm control. However, optimal heart rate during AF remains unknown. Aim of this analysis was to compare outcome between rate control above and below 80 beats per minute (bpm) in patients with persistent AF.

Methods

In the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study, 522 patients were included, 256 were randomized to rate control. This post-hoc analysis included patients randomized to rate control. Patients were divided according to their mean resting heart rate during follow up, <80 bpm (n=75) or ≥80 bpm (n=139). The endpoint, a composite of cardiovascular mortality, heart failure, thromboembolic complications, bleeding, pacemaker implantation and severe drug side effects, was compared between both groups.

Results

During follow-up (2.3±0.6 years) a significant difference between both groups in heart rate was observed (72±5 bpm vs. 90±8 bpm, p<0.001). Rate control drugs were not significantly different between both groups. NYHA class and fractional shortening remained unchanged in both groups. There were 17 (23%) endpoints in the low heart rate group and 24 (17%) in the higher heart rate group (absolute difference 5.4[-7.3-8.2], p=ns). Independent predictors for the primary endpoint were coronary artery disease, digoxin use and interrupted anticoagulation, not high heart rate. Quality of life was comparable in both groups during follow-up.

Conclusion

In patients treated with a rate control strategy no differences were observed in terms of cardiovascular morbidity, mortality and quality of life between the observed differences in level of rate control throughout follow-up.

Introduction

In many patients rate control is the first choice therapy of atrial fibrillation (AF).[1-4] However, the optimal heart rate during AF remains unknown.[5,6] The current American College of Cardiology/ American Heart Association /European Society of Cardiology guidelines on AF recommend a resting heart rate between 60-80 beats per minute (bpm) and a heart rate between 90-115 bpm during moderate exercise.[7] Management of rate control differs however.[8] Furthermore, randomized clinical trials investigating the optimal heart rate during AF are lacking.

Intuitively, strict rate control should be associated with fewer symptoms, better quality of life, lower incidence of heart failure, and as a consequence a better survival. Strict rate-control with more drugs and higher doses, on the other hand, could lead to drug-related adverse effects, causing symptomatic bradycardia, leading to falls, syncope, trauma, and preventable pacemaker implantation. The latter is supported by data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and a pooled analysis of the AFFIRM and RAte Control versus Electrical cardioversion (RACE) study.[6,9]

In the RACE study, the target heart rate in the rate control arm was a resting heart rate less than 100 bpm. The aim of the present post-hoc analysis of the RACE study was to compare rate control-randomized patients with an achieved mean resting heart rate <80 bpm versus patients with a mean heart rate ≥80 bpm during all follow-up visits with regard to long term outcome i.e. cardiovascular morbidity and mortality, quality of life and echocardiographic parameters.

Methods

Study design of the RACE study

The study design, patient characteristics and results of the RACE study have previously been published.[2] In short, 522 patients were included with recurrent persistent AF and randomized to either rate (n=256) or rhythm control (n=266). Patients were seen in the outpatient clinic 1, 3, 6, 12, 24 months after randomization and at the end of follow up (maximum of 3 years). At each visit cardiovascular events were documented and a 12-lead electrocardiogram was obtained. Aspirin (80 to 100 mg daily) was allowed in patients who were less than 65 years old and had lone AF. All other patients received oral anticoagulant therapy with acenocoumarol or fenprocoumon (target international normalized ratio (INR) 2.5 to 3.5).

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Study population

In the present analysis we included all patients randomized to rate control and having AF during the complete follow-up. In the RACE study cardioversion was allowed in patients randomized to rate control experiencing intolerable complaints of AF or unacceptable side effect of rate control medication or progressive left ventricular dysfunction. Alternatively, patients could be scheduled for atrioventricular node ablation and pacemaker implantation. Forty-two patients who were not continuously in AF during the total follow-up were therefore excluded. Of these patients 28 (67%) had a heart rate <80 bpm and 14 (33%) a heart rate >80 bpm. Mean heart rate was 75 bpm. Rate control was achieved with the administration of digitalis, a nondihydropyridine calcium-channel blocker, and a beta-blocker, alone or in combination.

The rate control target in the RACE study was a resting heart rate less than 100 bpm (monitored with a 12 lead resting electrocardiogram). In the RACE study no exercise test was performed to assess rate control. After randomization, patients were instituted on rate control medication to reach the target of a heart rate <100 bpm. Therefore, in this sub-analysis the adequacy of rate control was assessed at 1 month and subsequent visits until the end of study. Heart rate at baseline was not taken into account because adaptations of rate control medication was performed after baseline visit. Patients were assigned based on the mean heart rate over all subsequent follow-up visits (3 and 6 month, 1 year, 2 year and 3 year). Heart rate below (low heart rate) and above (high heart rate) 80 bpm during total follow-up was the designated boundary.

Table 1. Baseline characteristics

	Rate control mean HR <80 beats/min (n=75)	**Rate control mean HR ≥80 beats/min (n=139)**	**P Value**
Age (years)	70±8	68±10	0.09
Total AF duration (days)	662 (66-14909)	408 (14-4219)	0.04
Duration present episode of AF (days)	40 (2-399)	34 (1-392)	0.2
Atrial fibrillation - %	96	98	0.4
Atrial flutter - %	4	2	0.4
Symptoms of AF - %	72	71	0.8
Palpitations	29	25	0.5
Dyspnea	25	37	0.7
Fatigue	36	40	0.5
NYHA class for heart failure - %			
I	55	50	0.7
II	43	47	
III	2	3	

AF - atrial fibrillation; NYHA - New York Heart Association functional classification of heart failure

Endpoints

The primary end point was a composite of cardiovascular death, heart failure, thromboembolic complications, bleeding, severe adverse effects of antiarrhythmic drugs and pacemaker implantations. All events that occurred between randomization and the end of study were recorded. Definitions of the composites of the primary end point have been described before.[2] A committee of experts, who were unaware of the treatment assignments, adjudicated all reported end points.

Table 1. Baseline characteristics (continued)

	Rate control mean HR <80 beats/min	Rate control mean HR ≥80 beats/min	P Value
Underlying diesease - %			
Coronary artery diesease	27	27	0.9
Valve disease	21	17	0.3
Cardiomyopathy	5	17	0.02
Hypertension	45	39	0.3
No heart disease	19	22	0.6
Chronic obstructive pulmonary disease	23	22	0.3
Diabetes mellitus	9	12	0.5
Ischemic thrombo-embolic complication	27	11	0.003
Hemorrhagic complication	7	8	0.7
Treatment - %			
Digitalis	21	25	0.6
Beta-blocker	20	22	0.6
Verapamil or diltiazem	9	5	0.2
Digitalis and beta-blocker	24	22	0.6
Digitalis and calcium antagonist	15	18	0.5
Beta-blocker and calcium antagonist	4	3	0.5
Digitalis, beta-blocker, and calcium antagonist	-	1	0.2
No rate control drugs	7	4	0.4
ACE-inhibitor	24	25	0.9
ARB	9	7	0.5
Blood pressure - mm Hg			
Systolic	143±21	143±22	0.9
Diastolic	84±11	85±11	0.4

ACE - angiotensin converting enzyme; ARB - angiotensin II type I receptor blocker; HR - heart rate

Quality of life questionnaire

Quality of life was determined using the Dutch version of the Medical Outcomes Study Short-form health survey (SF-36) questionnaire as has been described before.[10] In short, the SF-36 contains items to assess physical health (general health perception, physical functioning, role limitations due to physical problems and bodily pain), as well as mental health (social functioning, role limitations due to emotional problems, mental health and vitality). Quality of life was assessed at baseline, after 1 year, and at the end of the study in 50 of the 75 patients (67%) with a mean heart rate <80 bpm and in 98 of 139 patients (71%) with a mean heart rate ≥80 bpm.

Statistica analysis

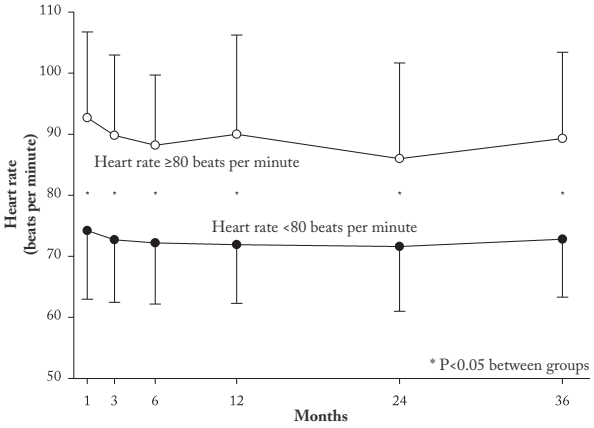
Baseline descriptive statistics are presented as mean ± standard deviation (SD) or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, in terms of patient characteristics, were evaluated by Students t-test or Mann-Whitney U-test, depending on normality of the data, for continuous data and by Fisher exact test or Chi-square test for categorical data. Kaplan Meier and Cox regression analyses were performed to assess the influence of mean heart rate during follow up on the occurrence of the primary endpoint and its components over time. Linearity of the continuous variables with respect to the response variable was assessed by determining the quartiles of their distribution. Thereafter hazard ratios for each quartile were calculated. In case of a linear trend in the estimated hazard ratios, the variable was introduced in the model as continuous. If no linearity was demonstrated, the variable was further categorized by taking together the quartiles with hazard ratios similar in magnitude, primarily the median value or otherwise based on clinical relevance. All patient characteristics, drug therapy, including interrupted oral anticoagulation use, blood pressure, atrial sizes and left-ventricular dysfunction at baseline were included. All univariate predictors with $p<0.1$ were tested in a multivariate model, using a stepwise approach. In the multivariate model a variable was excluded when $p\geq0.05$. In all analyses a value of $p<0.05$ was considered statistically significant. All analyses were performed according to the intention-to-treat principle.

Results

Patient characteristics

Twohundred-fourteen patients with permanent AF were included in this substudy. The low heart rate group consisted of 75 patients, 139 patients comprised the high heart rate group (Table 1). Baseline characteristics are listed in Table 1. In patients in the low-rate group duration of AF was longer and patients had more often endured an ischemic thromboembolic complication. No other differences were observed.

Figure 1. Mean heart rate during follow-up



Follow-up

Mean follow-up was 2.3±0.6 years. During total follow-up a significant difference in mean heart rate between both groups was observed (72±5 bpm, range 54–80 in the low versus 90±8 bpm, range 80–125 in the high heart rate group, p<0.001, Figure 1). NYHA class and blood pressure remained unchanged in both groups. From baseline to 3 years of follow-up, atrial sizes increased in both groups. No significant differences

Table 2. Echocardiographic measurements according to heart rate group

	Baseline	3 years	P Value
Left ventricular end systolic diameter			
<80 beats per minute	36±9	35±10	0.9
≥80 beats per minute	37±8	37±9	0.5
Left ventricular end diastolic diameter			
<80 beats per minute	52±7	52±9	0.6
≥80 beats per minute	53±7	53±8	0.7
Left atrial size, long axis view			
<80 beats per minute	45±7	46±8	0.2
≥80 beats per minute	45±6	47±6	0.1
Left atrial size, apical view			
<80 beats per minute	65±8	71±9	0.002
≥80 beats per minute	64±9	68±9	0.001
Right atrial size, apical view			
<80 beats per minute	59±8	66±10	0.02
≥80 beats per minute	57±9	64±10	<0.001

Table 2. Echocardiographic measurements (continued)

	Baseline	3 years	P Value
Fractional shortening			
<80 beats per minute	32±9	34±11	0.2
≥80 beats per minute	29±10	31±9	0.3
Septal wall thickness			
<80 beats per minute	11±2	11±3	0.6
≥80 beats per minute	10±2	10±2	0.2
Posterior wall thickness			
<80 beats per minute	10±2	10±2	0.5
≥80 beats per minute	9±2	10±2	0.4

were present between both groups at the end of follow up (Table 2). Also, no significant impairment of left ventricular function occurred in either group. All echo parameters were comparable between both groups during follow up. The type and combinations of rate control drugs did not differ between both groups (Table 3). In addition, no differences in the incidence of drug changes were observed (data not shown). The use of anticoagulation was interrupted in 28 (13%) of all patients (7 [9%] in the low versus 21 [15%] in the high heart rate group, p=0.3), because of (non)cardiac surgery or presence of lone AF.

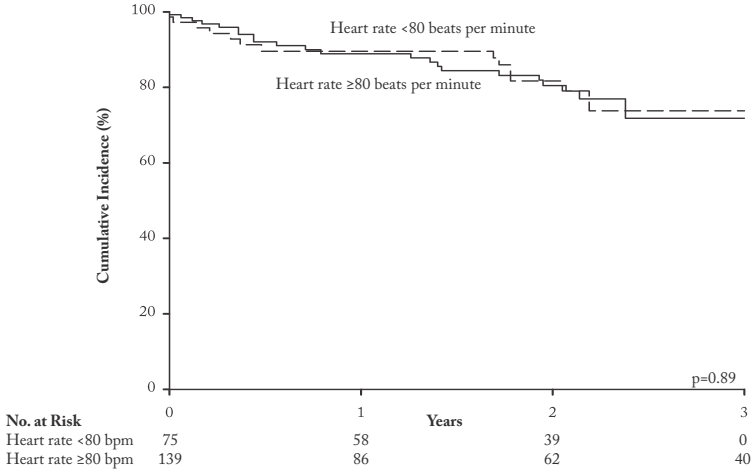
Cardiovascular morbidity and mortality

The primary end point occurred in 17 patients (23%) in the low heart rate group versus 24 patients (17%) in the high heart rate group (Table 4, Figure 2).No significant differences in cardiovascular mortality were observed between both groups.

Table 3. Combinations of rate control drugs during follow-up

	Baseline		End of study	
Type of rate control drugs (%)	<80 beats per minute	≥80 beats per minute	<80 beats per minute	≥80 beats per minute
Digitalis	21	25	11	23
Beta-blocker	20	22	16	19
Verapamil	9	5	13	7
Digitalis and beta-blocker	24	22	24	27
Digitalis and verapamil	15	18	20	15
Beta-blocker and verapamil	4	3	4	1
Digitalis, beta-blocker, and verapamil	-	1	7	6
No rate control drugs	7	4	4	2

Figure 2. Kaplan-Meier estimates according to heart rate group



Hospitalization for heart failure, thromboembolic complications and bleeding occurred in similar proportions in both groups. In both groups one severe adverse effect of rate control drugs was observed, AV nodal escape rhythm due to digoxin intoxication in the low heart rate group and symptomatic bradycardia with AV nodal escape rhythm during beta-blocker therapy in combination with digoxin in the high heart rate group. In the high heart rate group three patients were treated with atrioventricular node ablation and pacemaker implantation because of intolerable symptoms of AF.

Table 4. Incidence of the primary endpoint and its components

	Mean heart rate <80 beats per minute	Mean heart rate ≥80 beats per minute	Absolute difference
End point	17 (23)	24 (17)	5.4 (-7.3-18.2)
Deaths from cardiovascular cause	5 (7)	9 (7)	0.2 (-7.0-7.4)
Sudden death	2 (3)	4 (3)	-0.2 (-4.9-4.4)
Heart failure	1 (1)	2 (1)	-0.1 (-3.4-3.2)
Thromboembolic complication	-	-	-
Bleeding	2 (3)	3 (2)	0.5 (-3.9-4.9)
Heart failure	4 (5)	3 (2)	3.2 (-5.3-8.9)
Thromboembolic complication	5 (7)	7 (5)	1.6 (-5.3-8.6)
Bleeding	5 (7)	6 (4)	2.4 (-2.4-9.1)
Severe adverse effects antiarrhythmic drugs	1 (1)	1 (1)	0.6 (-2.4-3.6)
Pacemaker implantation	-	3 (2)	-2.2 (-4.6-0.3)

Table 5. Uni- and multivariate predictors of primary outcome

	Hazard ratio univariate (95% CI)	P Value	Hazard ratio multivariate (95% CI)	P Value
Mean heart rate ≥80 beats per minute	1.0 (0.5-2.1)	0.9	1.03 (0.5-2.1)	0.9
Coronary artery disease	3.1 (1.6-6.1)	0.001	3.8 (1.9-7.6)	<0.001
Digoxin use during study	2.4 (0.9-6.2)	0.06	2.8 (1.1-7.4)	0.03
Interrupted OAC use	2.0 (0.9-4.7)	0.08	2.4 (1.0-5.6)	0.04
Valvular heart disease	2.2 (1.1-4.5)	0.03	-	
Previous bleeding	2.5 (1.0-6.6)	0.05	-	
Reduced fractional shortening	0.5 (0.3-1.1)	0.09	-	

CI - confidence interval; OAC oral anticoagulation

We identified, by multivariate Cox regression analyses, coronary artery disease, the use of digoxin and interrupted oral anticoagulation use as independent predictors of cardiovascular morbidity and mortality (Table 5), but not mean heart rate ≥80. In addition, no influence of the mean heart rate divided on the median value (83 bpm), instead of 80 bpm, was found (data not shown).

Quality of life

Quality of life was comparable between both groups at baseline and during follow up. No important changes in quality of life occurred in both groups (Table 6). Also no differences between both groups were found in regard to complaints of AF (data not shown).

Discussion

This post-hoc analysis of the RACE study shows no differences in cardiovascular morbidity and mortality and quality of life between patients having a higher or lower heart rate during AF. Therefore, it suggests that differences in the level of rate control observed in this post-hoc analysis do not influence outcome in patients with permanent AF. Instead, prognosis seems determined by the underlying cardiovascular disease, the use of digoxin and interrupted use of oral anticoagulation. Furthermore, no differences in quality of life and changes in left ventricular function nor atrial sizes between both levels of rate control were observed.

Heart rate during rate control strategy and prognosis

In many patients rate control is the first choice therapy in AF, also in patients with heart failure.[3] Data on the level of rate control, however, are limited. The effect of heart rate on cardiovascular morbidity and mortality, and quality of life has not been studied before in randomized trials. For the levels of rate control observed in the present

Table 6. SF-36 quality of life scores (mean)

SF-36 Subscale	Heart rate - beats per minute	Baseline	End of study	Change over study
General health	<80	58±19	59±17	0
	≥80	54±18	56±18	3
Physical functioning	<80	64±24	59±24	-5
	≥80	62±25	58±25	-4
Role physical	<80	50±46	56±47	5
	≥80	48±46	51±43	4
Bodily pain	<80	80±20	80±33	0
	≥80	81±23	78±23	-2
Mental health	<80	77±16	79±16	3
	≥80	75±18	75±18	2
Social functioning	<80	79±23	84±22	5
	≥80	78±22	79±22	2
Role emotional	<80	77±39	73±41	-5
	≥80	72±42	73±39	2
Vitality	<80	65±22	63±17	-2
	≥80	60±21	57±23	-3

analysis (mean 72 bpm versus a mean of 90 bpm), this post-hoc analysis of RACE study suggests that rate control according to the current guidelines is not superior to a heart rate above the recommended frequency.

In a previous post-hoc analysis we compared data from AFFIRM and RACE, since these trials used different definitions of adequate rate control.[6] In AFFIRM adequate rate control was defined as a resting heart rate below 80 bpm and either a maximum heart rate during a 6-minute walk test below 110 bpm or an average heart rate during 24-hour Holter ECG monitoring below 100 bpm and no heart rate above 110% of maximum predicted heart rate.[1] In RACE a more lenient approach was used, a resting heart rate below 100 bpm. This analysis of the comparison between both studies suggested that the stringency of rate control does not influence mortality and cardiovascular morbidity.[6]

Stringent rate control, as performed in AFFIRM, was associated with similar rates of a composite endpoint of major clinical events and with similar overall survival rates but with more pacemaker implantations.[6] In 5.3% of included patients of AFFIRM a pacemaker-implantation and atrioventricular node ablation was performed to obtain adequate rate control. In an additional 7.3% of patients a pacemaker implantation was performed for symptomatic bradycardia. In only 1.2% of the patients in the RACE study, however, pacemaker implantation and atrioventricular node ablation occurred.

Data from the AFFRIM showed that strict rate control was difficult to achieve. It could be achieved successfully in two thirds of the patients.[9] Strict rate control though may be, beneficial in selected patient groups. Khand et al. observed that in patients with an impaired left ventricular function and AF, a more strict rate control approach may be beneficial.[11] They randomized patients with heart failure (left ventricular ejection fraction averaging 24%) and AF to carvedilol plus digoxin or to digoxin alone. After a follow-up of 4 months, heart rate was significantly lower in the patients treated with the combination of drugs, compared to the patients who were treated with digoxin alone. Compared to placebo, the addition of carvedilol to digoxin significantly improved left ventricular ejection fraction (24±7% to 31±10%, $p<0.05$). In contrast to the findings of Khand et al, an observational study by Rienstra et al. found that a lower heart rate was associated with a poorer prognosis. This cohort also had a reduced LVEF (23±8%) and AF.[12] Whether the observation by Khand et al. is due to heart rate control itself or a salutary effect of beta-blockade in patients with congestive heart failure cannot be determined. Furthermore, whether such more stringent heart rate control translates into a survival benefit and reduced morbidity remains to be seen. In this respect, Fauchier et al. recently showed that patients with AF and heart failure who were treated with beta-blocker therapy showed a significant lower mortality compared to a control group who were not treated with beta-blockers.[13] Furthermore, they also showed that patients on digoxin alone had a worse survival than patients on beta-blockers (with or without digoxin), similar to patients without rate control drugs. In this respect it is noteworthy that in our analysis the use of digoxine also deteriorated prognosis.

The low occurrence of serious adverse effects of rate control drugs in the present analysis is noteworthy. In the rate control group of the RACE study no pacemakers were implanted because of bradycardias. Amiodarone can also be used for rate control. In the RACE study this was discouraged because of (non)cardiac side effects. Dronedarone, a new antiarrhythmic drug based on amiodarone is well tolerated, with no organ toxicities or proarrhythmia, may become an additional drug to control ventricular rate during AF in the near future.[14] Compared with placebo, the mean reduction with dronedarone was 12 bpm during 24 hours ($p<0.0001$) and of 25 bpm during maximal exercise ($p<0.0001$). It also successfully reduced the heart rate at the moment of a relapse of AF.[15]

Heart rate and quality of life

Quality of life is reduced in patients with AF.[16,17] Maintenance of sinus rhythm is associated with improvement of quality of life.[18,19] Quality of life, however, is comparable between rhythm and rate control strategies.[16,20] This study shows that there are no differences in quality of life between a high and low level of rate control.

Heart rate and left ventricular function and atrial diameters

No data are available on left ventricular function and atrial sizes in patients treated with different stringencies of rate control. The present study observed no differences in echocardiographic parameters between both groups.

Predictors for cardiovascular morbodoty and mortality

The strongest independent predictor for the composite endpoint was the presence of coronary artery disease. Post-hoc analysis of the AFFIRM[21] and RACE[4] also showed that the presence of coronary artery disease was associated with prognosis in patients with AF. Outcome of this analysis underlines that the focus in patients with AF should not be on heart rate but on underlying heart disease.

Interrupted use of oral anticoagulation was identified as another independent predictor of prognosis. In 28 patients of the present cohort anticoagulation was interrupted (7 in the low vs. 21 in the high heart rate group) because of (non)cardiac surgery or presence of lone AF. According to the guidelines oral anticoagulation is nowadays prescribed according to the $CHADS_2$ risk score and is continued independent of the rhythm. At the moment the RACE study was conducted, after acceptance of AF patients discontinued oral anticoagulation and started aspirin in case of absence of risk factors. (Re-)initiation of oral anticoagulation increases the risk of bleeding. In the ACTIVE W trial a lower risk of major bleeding was seen in patients already on anticoagulation, randomized to oral anticoagulation, compared to patients not already on this treatment.[22] In accordance with this finding, the ISCOAT study showed that bleeding risk was increased during the first 90 days of treatment.[23] These imbalanced situations might explain the increased risk of mortality and morbidity caused by interrupted oral anticoagulation use.

Not only the stringency of heart rate reduction but also the medication instituted to achieve adequate rate control is controversial. The positive effect of beta-blockers in heart failure is indisputable in patients with sinus rhythm.[24] It is, however, unknown whether heart rate reduction with digoxin also improves survival. Patients with sinus rhythm and heart failure have no survival benefit with the use of digoxin.[25] It is furthermore suggested that digoxin increases mortality in patients with AF.[26] The present post-hoc analysis of the RACE study confirms the negative association between digoxin use and prognosis. The increased risk on cardiovascular morbidity and mortality in patients treated with digoxin remains difficult to explain, especially in this population without severe heart failure. More data on this issue are certainly warranted.

Limitations

In the RACE study adequate rate control was defined by resting heart rate on a 12 lead ECG. No evaluation of rate control during exercise was performed. Furthermore no 24-hour Holter ECG registration was performed which precludes evaluation of rate control during the whole day. Therefore data on rate control during the day and

during exercise are lacking. In RACE follow-up was limited to 3 years. In this post-hoc analysis patients were divided according to the mean heart rate during follow up, no randomization was performed to either a strict or lenient approach of rate control. Furthermore, the number of included patients in this post-hoc analysis is limited. Considering the non randomized design of this study, the limited sample size and restricted follow-up, no definite conclusions can be made on how to treat patients according to a rate control strategy. These issues can only be resolved with randomized trials assessing different rate control strategies.

Conclusion

In patients treated according to rate control strategy no differences were observed between patients with high or low heart rate in terms of cardiovascular morbidity, mortality and quality of life. Randomized studies, e.g. RACE II, assessing stringency of rate control are eagerly awaited.[5]

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Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

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Abstract

Introduction

Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

Methods

We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict ratecontrol strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of followup was at least 2 years, with a maximum of 3 years.

Results

The estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group, with an absolute difference with respect to the lenient-control group of −2.0 percentage points (90% confidence interval, −7.6 to 3.5; P<0.001 for the prespecified noninferiority margin). The frequencies of the components of the primary outcome were similar in the two groups. More patients in the lenient-control group met the heart-rate target or targets (304 [97.7%], vs. 203 [67.0%] in the strict-control group; P<0.001) with fewer total visits (75 [median, 0], vs. 684 [median, 2]; P<0.001). The frequencies of symptoms and adverse events were similar in the two groups.

Conclusion

In patients with permanent atrial fibrillation, lenient rate control is as effective as strict rate control and is easier to achieve.

Introduction

Atrial fibrillation is not a benign condition.[1] It may cause symptoms and is associated with stroke and heart failure. Previous studies have established that the rates of complications and death were similar in patients with atrial fibrillation receiving rate-control therapy and in those receiving rhythm-control therapy.[2,3] Therefore, rate control has become front-line therapy in the management of atrial fibrillation. The optimal level of heart-rate control, however, is unknown, as is whether strict rate control is associated with an improved prognosis as compared with a more lenient approach.[2-6] Guidelines, though empirical and not evidence-based, recommend the use of strict rate control[1] to reduce symptoms, improve the quality of life and exercise tolerance, reduce heart failure (and hence bleeding[7] and stroke[8]), and improve survival. On the other hand, strict rate control could cause drug-related adverse effects, including bradycardia, syncope, and a need for pacemaker implantation. Thus, the balance between benefit and risk in terms of cardiovascular morbidity and mortality, quality of life, exercise tolerance, and disease burden remains unknown. Therefore, we conducted a multicenter, prospective, randomized trial to test the hypothesis that lenient rate control is not inferior to strict rate control in preventing cardiovascular events in patients with permanent atrial fibrillation.

Methods

Study design

The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) study was a prospective, multicenter, randomized, open-label, noninferiority trial designed to compare two ratecontrol strategies in patients with permanent atrial fibrillation. The design of the study has been described previously.[6] Recruitment started in January 2005 and ended in June 2007.

The study was initiated and coordinated by the Interuniversity Cardiology Institute of the Netherlands, the University Medical Center Groningen, and the Working Group on Cardiovascular Research the Netherlands. The study was funded by a major grant from the Netherlands Heart Foundation and by unrestricted educational grants from pharmaceutical and device companies. None of the sponsors were involved in the study design, data collection, data analysis, or manuscript preparation. The steering committee was responsible for the design and conduct of the study, the data analysis and reporting, and manuscript preparation. Study monitoring, data management, and validation were independently performed at the Trial Coordination Center (University Medical Center Groningen, the Netherlands). The study was approved by the institutional review boards of all participating centers. All authors reviewed a previous version of the manuscript and vouch for the accuracy and completeness of the data and analyses.

Study participants

The study was conducted in 33 centers in the Netherlands. Eligibility criteria were as follows: permanent atrial fibrillation for up to 12 months, age of 80 years or younger, mean resting heart rate above 80 beats per minute, and current use of oral anticoagulation therapy (or aspirin, if no risk factors for thromboembolic complications were present). Reasons for exclusion were described previously.[6]

Randomization and treatment

After providing written informed consent, all trial participants were randomly assigned, in an open label fashion, to undergo either a lenient rate-control strategy or a strict rate-control strategy. Randomization was accomplished by means of a central, interactive, automated telephone system, with the use of permuted blocks of various sizes.

During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs (i.e., beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved. Patients assigned to undergo the lenient-control strategy (which allowed for a higher heart-rate target than strict control) had a target resting heart rate of below 110 beats per minute. Patients assigned to undergo the strict-control strategy had a target resting heart rate of below 80 beats per minute — lower than the target in the lenient control group — and a target heart rate of below 110 beats per minute during moderate exercise. The resting heart rate was measured in both groups by means of 12-lead electrocardiography after 2 to 3 minutes of rest in the supine position. In the strict-control group only, the heart rate during exercise was measured during moderate exercise performed for a duration corresponding to 25% of the maximal time achieved on bicycle exercise testing. After the heart-rate targets were reached, 24-hour Holter monitoring was performed to check for bradycardia, in the strict control group only.

Follow-up outpatient visits occurred every 2 weeks until the heart-rate target or targets were achieved and in all patients after 1, 2, and 3 years. Follow-up was terminated after a maximum follow-up period of 3 years or on June 30, 2009, whichever came first.

During the follow-up period, the resting heart rate (and the exercise heart rate, in the strict-control group) was assessed by the attending physician at each visit. If rate-control drugs had to be adjusted, 24-hour Holter monitoring was repeated to check for bradycardia, in the strict-control group only. If the heart-rate target or targets could not be achieved or patients remained symptomatic, the study protocol permitted further adjustment of rate-control drugs or doses, electrical cardioversion, or ablation at the discretion of the attending physician.

Outcomes

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, major bleeding, and arrhythmic events including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate-control drugs, and implantation of a pacemaker or cardioverter–defibrillator. Secondary outcomes included the components of the primary outcome, death from any cause, symptoms, and functional status. All reported primary-outcome events were adjudicated by an independent adjudication committee that was unaware of the randomized treatment assignments. Only deaths classified as having a cardiac arrhythmic, cardiac nonarrhythmic, or noncardiac vascular cause were included in the analysis of the primary end point.[9,10]

Heart failure was defined as heart failure necessitating hospitalization and the start of or increase in dose of diuretics. Stroke was defined as the sudden onset of a focal deficit consistent with occlusion of a major cerebral artery (documented by means of imaging) and categorized as ischemic, hemorrhagic, or indeterminate. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ as documented with the use of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level by at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Syncope was defined as a transient loss of consciousness that may have been caused by a rhythm disorder. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting more than 30 seconds or requiring electrical termination owing to hemodynamic compromise. Cardiac arrest was defined as circulatory arrest necessitating resuscitation and hospitalization. Life-threatening adverse effects of rate-control drugs included digitalis intoxication and conduction disturbances necessitating hospitalization. Pacemaker implantations for clinically significant bradycardia and cardioverter–defibrillator implantations for sustained ventricular arrhythmias were the only types of implantations included in the primary analysis.

Statistical analysis

The trial was designed to determine whether a strategy of lenient rate control was as effective as (i.e., noninferior to) a strategy of strict rate control. The study size was determined on the basis of an expected rate of the primary outcome of 25% at 2.5 years in both treatment groups and a requirement that the study had 80% power to rule out an absolute increase of 10 percentage points in the rate of the primary outcome at 2.5 years in the lenient-control group, with a one-sided alpha level of 0.05. Pretrial estimates of the expected event rates were based on the observed event rate in the (lenient) rate-control group of the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial.[3] The noninferiority boundary in the present study was similar to that in the previous RACE trial, which implied that noninferiority of lenient rate control to strict rate control was to be determined by the same criteria by which we had previously shown the noninferiority of (lenient)

Table 1. Baseline characteristics

	Lenient rate control (n=311)	Strict rate control (n=303)	Total population (n=614)
Age - yr	69±8	67±9	68±8
Male sex - no. (%)	205 (65.9)	198 (65.3)	403 (65.6)
Duration of any atrial fibrillation - mo			
Median	16	20	18
Interquartile range	6-54	6-64	6-60
Duration of permanent atrial fibrillation - mo			
Median	3	2	3
Interquartile range	1-6	1-5	1-6
Previous electrical cardioversion - no (%)	221 (71.1)	220 (72.6)	441 (71.8)
Hypertension	200 (64.3)	175 (57.8)	375 (61.1)
Coronary artery disease	67 (21.5)	44 (14.5)	111 (18.1)
Valvular heart disease	64 (20.6)	60 (19.8)	124 (20.2)
Chronic obstructive pulmonary disease	36 (11.6)	43 (14.2)	79 (12.9)
Diabetes mellitus	36 (11.6)	32 (10.6)	68 (11.1)
Lone atrial fibrillation†	5 (1.6)	6 (2.0)	11 (1.8)
Previous hospitalization for heart failure	28 (9.0)	32 (10.6)	60 (9.8)
$CHADS_2$ score‡	1.4±1.0	1.4±1.2	1.4±1.1
0 or 1	178 (57.2)	195 (64.4)	373 (60.7)
2	94 (30.2)	65 (21.5)	159 (25.9)
3-6	39 (12.5)	43 (14.2)	82 (13.4)
Symptoms – no. (%)	173 (55.6)	175 (57.8)	348 (56.7)
Palpitations	62 (19.9)	83 (27.4)	145 (23.6)
Dyspnea	105 (33.8)	109 (36.0)	214 (34.9)
Fatigue	86 (27.7)	97 (32.0)	183 (29.80)
Body mass index – kg/m2	29±5	29±5	29±5
Blood pressure – mmHg			
Systolic	137±19	135±16	136±18
Diastolic	85±11	82±11	83±11
Heart rate in rest – beats per minute	96±14	96±12	96±13

† Lone atrial fibrillation was defined as atrial fibrillation in the absence of cardiovascular disease and extracardiac precipitating causes of atrial fibrillation.

‡ The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing al the points for a given patient.[8]

Table 1. Baseline characteristics (continued)

	Lenient rate control (n=311)	Strict rate control (n=303)	Total population (n=614)
New York Heart Association functional class			
I – no. (%)	206 (66.2)	194 (64.0)	400 (65.1)
II – no. (%)	89 (28.7)	96 (31.7)	185 (30.2)
III – no. (%)	16 (5.1)	13 (4.3)	29 (4.7)
Rate control medications in use – no. (%)			
No rate control drugs	36 (11.6)	27 (8.9)	63 (10.3)
Beta-blocker alone	140 (45.0)	136 (44.9)	276 (45.0)
Verapamil/diltiazem alone	18 (5.8)	19 (6.3)	37 (6.0)
Digoxin alone	20 (6.4)	24 (7.9)	44 (7.2)
Beta-blocker + verapamil/diltiazem	7 (2.3)	11 (3.6)	18 (2.9)
Beta-blocker + digoxin	53 (17.0)	49 (16.2)	102 (16.6)
Verapamil/diltiazem + digoxin	14 (4.5)	14 (4.6)	28 (4.6)
Beta-blocker + verapamil/diltiazem + digoxin	2 (0.6)	5 (1.7)	7 (1.1)
Sotalol	18 (5.8)	13 (4.3)	31 (5.0)
Amiodarone	3 (1.0)	5 (1.7)	8 (1.3)
Other medications in use at baseline – no. (%)			
ARB or ACE inhibitor	166 (53.4)	140 (46.2)	306 (49.8)
Diuretic	134 (43.1)	113 (37.3)	247 (40.2)
Statin#	103 (33.1)	74 (24.4)	177 (28.8)
Vitamin K antagonist	308 (99.0)	298 (98.3)	606 (98.7)
Aspirin	4 (1.3)	6 (2.0)	10 (1.6)
Echocardiographic parameters – mm			
Left atrial size, long axis	46±6	46±7	46±7
Left ventricular end-diastolic diameter	51±7	51±8	51±7
Left ventricular end-systolic diameter	36±8	36±9	36±8
Left ventricular ejection fraction – %	52±11	52±12	52±12
≤ 40% – no. (%)	45 (14.5)	48 (15.8)	93 (15.1)

ARB denotes angiotensin-receptor blocker, and ACE angiotensin-converting enzyme.
Statins are defined here as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.

rate control to rhythm control. A sample size of 250 patients in each group with a median follow-up of 2.5 years satisfied the statistical requirements, allowing for an attrition rate of less than 5% of patients. In the course of the trial, we found that the primary outcome occurred less frequently than anticipated. We increased the number of patients to 300 in each group and extended the follow-up period to June 30, 2009, with a maximum duration of 3 years.

The primary analysis for efficacy (in the intention-to-treat population) consisted of a comparison between the lenient-control group and the strict-control group of the time to the first occurrence of the composite primary outcome as assessed by Kaplan–Meier curves. The follow-up data were censored for patients who had a first occurrence of one of the primary-outcome events, had informed consent withdrawn, had died from a noncardiovascular cause, were lost to follow-up, had been in the trial for 3 years, or had been followed through June 30, 2009 — whichever event came first. The observation time was calculated as the time from randomization until either the occurrence of the primary outcome or the moment of censoring.

To satisfy the criterion for noninferiority, the upper bound of the 90% confidence interval for the absolute difference between the two treatment groups in the estimated rate of the primary outcome needed to be less than 10 percentage points (erroneously specified in our design paper as a relative 10% difference, when in fact it is a 10-percentage-point absolute difference[6]). Because the treatment period had been extended, we eventually used the estimated cumulative incidences at 3 years to assess noninferiority.

The difference between the two groups in the 3-year cumulative incidence was calculated by subtracting the Kaplan–Meier estimated event rate in the lenient-control group from that in the strict control group. The 90% confidence interval for the difference was calculated with the use of the standard errors from the Kaplan–Meier curves. We also tested for noninferiority by comparing the upper bound of the 90% confidence interval for the hazard ratio (calculated from the Cox proportional-hazards model) for the primary outcome in the lenient-control group as compared with the strict-control group with a margin of 1.40, which was derived (post hoc) as 25% divided by (25% + 10%). There were no prespecified subgroup analyses. The results of post hoc subgroup analyses are presented for descriptive purposes. No formal interim analyses were planned or performed. The data and safety monitoring board monitored the occurrence of clinical events from the standpoint of safety.

Results

Patients

A total of 614 patients were enrolled in the study: 311 in the lenient-control group and 303 in the strict-control group (Table 1 and Fig. 1). The groups were well matched, with the exception of a higher prevalence of coronary artery disease and statin use, and a slightly higher diastolic pressure, in the lenient-control group.

Figure 1. Randomization and follow-up of the study patients

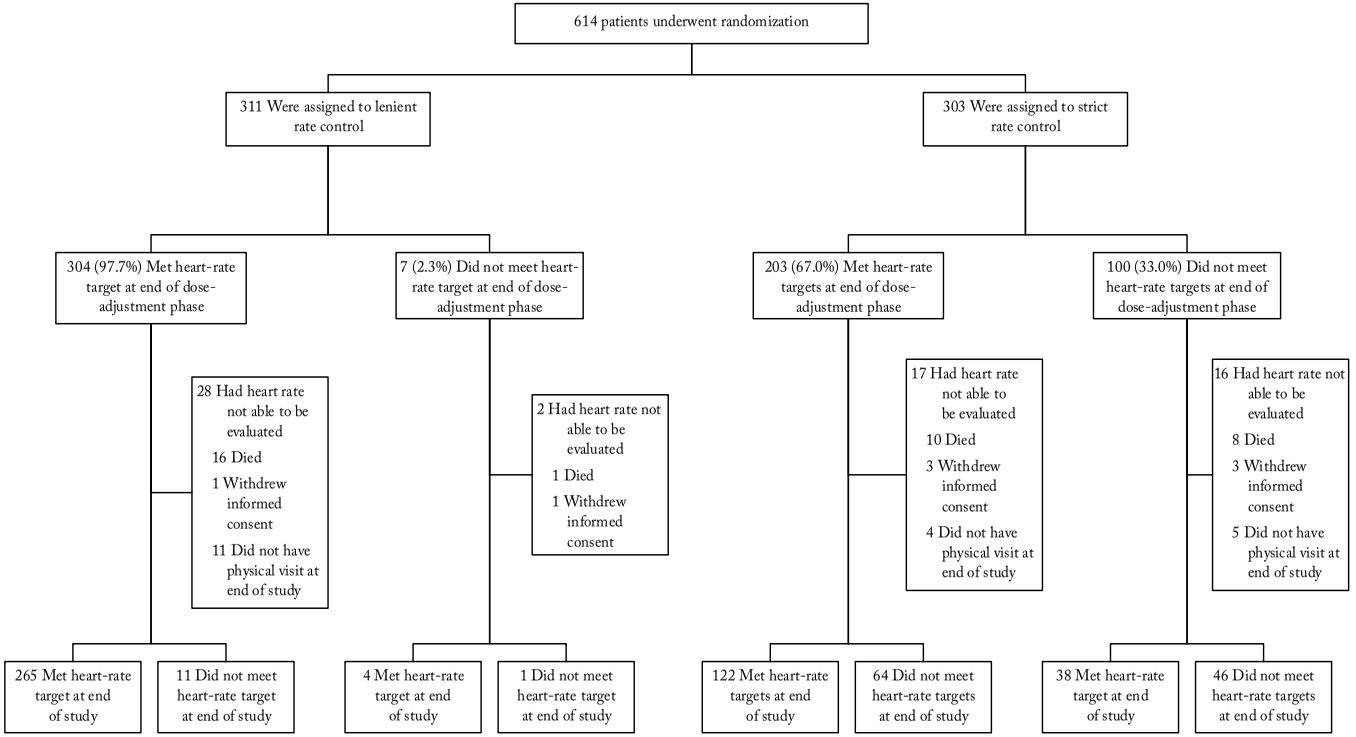


Table 2. Rate control targets and drug therapy at the end of the dose-adjustment-phase, according to treatment group

	Lenient rate control (n=311)	Strict rate control (n=303)	P Value
Rate control target or targets achieved - no (%)	304 (97.7)	203 (67.0)	<0.001
Resting heart rate – no.(%)			
< 70 beats/min	1 (0.3)	67 (22.1)	<0.001
70 to 80 beats/min	5 (1.6)	161 (53.1)	<0.001
81 to 90 beats/min	112 (36.0)	39 (12.9)	<0.001
91 to 100 beats/min	123 (39.5)	20 (6.6)	<0.001
>100 beats/min	70 (22.5)	16 (5.3)	<0.001
Resting heart-rate target achieved – no.(%)	304 (97.7)	228 (75.2)	<0.001
Exercise heart-rate achieved – no.(%)		220 (72.6)	
Mean heart rate – beats/min		99±16	
Mean duration of exercise with target achieved – sec		94±44	
Holter monitoring			
Mean heart rate – beats per minute		78±11	
Maximal RR interval – seconds		2.3±0.6	
Visits to achieve rate control target – no.	75	684	<0.001
Median	0	2	
Interquartile range	0-0	1-3	
Reasons failure rate control target– no. (%)			<0.001
Drug related adverse events	0/7	25/100 (25.0)	
No or acceptable complaints	7 (100)	53/100 (53.0)	
Target impossible to achieve with drugs	0/7	22/100 (22.0)	
Rate control medication – no. (%)			
No rate control drugs	32 (10.3)	3 (1.0)	<0.001
Beta-blocker alone	132 (42.4)	61 (20.1)	<0.001
Verapamil/diltiazem alone	18 (5.8)	16 (5.3)	0.78
Digoxin alone	21 (6.8)	5 (1.7)	0.002
Beta-blocker + verapamil/diltiazem	12 (3.9)	38 (12.5)	<0.001
Beta-blocker + digoxin	60 (19.3)	113 (37.3)	<0.001
Verapamil/diltiazem + digoxin	18 (5.8)	29 (9.6)	0.08
Beta-blocker + verapamil/diltiazem + digoxin	3 (1.0)	27 (8.9)	<0.001

Table 2. Rate control targets and drug therapy at the end of the dose-adjustment-phase, according to treatment group (continued)

	Lenient rate control (n=311)	Strict rate control (n=303)	P Value
Rate control medication dose - mg. (no.)			
Beta-blocker (adjusted to metoprolol)	120±78 (210)	162±85 (243)	<0.001
Verapamil	166±60 (46)	217±97 (105)	<0.001
Diltiazem	232±74 (5)	217±64 (7)	0.72
Digoxin	0.19±0.8 (109)	0.21±0.8 (180)	0.06

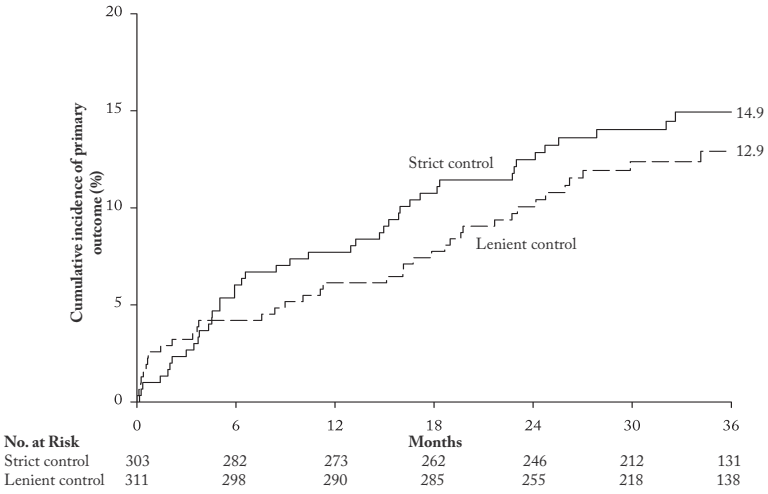
Heart rates

Data recorded at the end of the dose-adjustment phase are reported in Table 2. The mean (±SD) resting heart rate at the end of the dose-adjustment phase was 93±9 beats per minute in the lenientcontrol group, as compared with 76±12 beats per minute in the strict-control group (P<0.001). After 1 and 2 years and at the end of the follow-up period, the resting heart rates in the lenient-control group were 86±15, 84±14, and 85±14 beats per minute, respectively, as compared with 75±12, 75±12, and 76±14 beats per minute, respectively, in the strict-control group (P<0.001 for all comparisons between the two groups). During the follow-up period, 18 patients in the lenient-control group and 22 patients in the strict-control group had conversion to sinus rhythm (P = 0.60). Nine patients in both groups were in sinus rhythm at the end of follow-up (P = 0.96). There was no difference between the two groups in the mean percentage of the study period during which the international normalized ratio was within the target range.

Primary outcome

A total of 81 patients (38 in the lenient-control group and 43 in the strict-control group) reached the primary outcome. Kaplan–Meier curves for the primary outcome are shown in Figure 2. The 3-year estimated cumulative incidence was 12.9% in the lenient-control group and 14.9% in the strict control group (Table 3), with an absolute difference between lenient control and strict control of −2.0 percentage points (90% confidence interval [CI], −7.6 to 3.5) and a hazard ratio of 0.84 (90% CI, 0.58 to 1.21). As compared with strict rate control, lenient rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk (P<0.001) and the hazard ratio (P = 0.001). The hazard ratio was 0.80 (90% CI, 0.55 to 1.17) after statistical adjustment for the unbalanced distribution of the presence of coronary artery disease, the use of statins, and the diastolic blood pressure. The cumulative incidences of components of the primary outcome are shown in Table 3.

Figure 2. Kaplan-Meier estimates of the cumulative incidence of the primary outcome



Other outcomes

Death from any cause occurred in 17 patients in the lenient-control group (5.6% at 3 years), as compared with 18 (6.6% at 3 years) in the strict-control group (hazard ratio 0.91; 90% CI, 0.52 to 1.59). Death from noncardiovascular causes occurred in 8 patients in the lenient-control group as compared with 7 in the strict-control group.

At the end of the follow-up period, 129 of 283 patients (45.6%) in the lenient-control group and 126 of 274 patients (46.0%) in the strict-control group had symptoms associated with atrial fibrillation (P = 0.92): dyspnea (30.0% vs. 29.6%, P = 0.90), fatigue (24.4% vs. 22.6%, P = 0.63), and palpitations (10.6% vs. 9.5%, P = 0.66). In addition, at the end of the follow-up period, in the lenient-control group and the strict-control group, 70.0% and 70.4% of patients, respectively, were in New York Heart Association functional class I, 23.3% and 23.4% were in class II, and 6.7% and 6.2% were in class III (P = 0.74 for all comparisons). Frequencies of hospitalizations and adverse events were similar in the two groups (Table 4).

Subgroups analysis

Among the 241 patients with a $CHADS_2$ score of 2 or more, the primary outcome occurred in 17 of the 133 patients in the lenient-control group and in 25 of the 108 patients in the strict-control group (P<0.001 for noninferiority). Among the 373 patients with a $CHADS_2$ score below 2, the primary outcome occurred in 21 of the 178 patients in the lenient-control group and in 18 of the 195 patients in the strict-control group (P = 0.02 for noninferiority). The primary outcome event rates were similar across heart-rate categories at the end of the dose-adjustment phase (Table 5).

Table 3. Cumulative incidence of the composite primary outcome and its components

	Lenient rate control (n=311)	Strict rate control (n=303)	Hazard ratio (90% CI)
	no. of patients (%)		
Composite primary outcome	38 (12.9)	43 (14.9)	0.84 (0.58 – 1.21)
Individual components			
Death from cardiovascular cause	9 (2.9)	11 (3.9)	0.79 (0.38 – 1.65)
From cardiac arrhythmia	3 (1.0)	4 (1.4)	
From cardiac cause, no arrhythmia	1 (0.3)	2 (0.8)	
From noncardiac vascular cause	5 (1.7)	5 (1.9)	
Heart failure	11 (3.8)	11 (4.1)	0.97 (0.48 – 1.96)
Stroke	4 (1.6)	11 (3.9)	0.35 (0.13 – 0.92)
Ischemic	3 (1.3)	8 (2.9)	
Hemorrhagic	1 (0.3)	4 (1.5)	
Systemic embolism	1 (0.3)	0	
Bleeding	15 (5.3)	13 (4.5)	1.12 (0.60 – 2.08)
Intracranial	0	3 (1.0)	
Extracranial	15 (5.3)	10 (3.5)	
Syncope	3 (1.0)	3 (1.0)	
Life threatening AE of rate control drugs	3 (1.1)	2 (0.7)	
Sustained VT or VF	0	1 (0.3)	
Cardioverter-defibrillator implantation	0	1 (0.4)	
Pacemaker implantation	2 (0.8)	4 (1.4)	

AE - adverse event; CI - confidence Interval; VT - ventricular tachycardia; VF - ventricular fibrillation

Discussion

We found that lenient rate control was noninferior to strict rate control in the prevention of major cardiovascular events in patients with permanent atrial fibrillation. The primary outcome occurred in 12.9% of patients in the lenient-control group, as compared with 14.9% of patients in the strict-control group. The heart rates achieved in the strict-control group were similar to those observed in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.[11] We confirmed a post hoc comparison of data from the AFFIRM study and the first RACE trial, demonstrating that the stringency of rate control was not associated with significant differences in outcome.[2,3,5]

Table 4. Hospitalization and adverse events

	Lenient rate control (n=311)	Strict rate control (n=303)	P Value
Hospitalizations	78 (25.1)	83 (27.4)	0.5
Hospitalization for cardiac surgery	5 (1.6)	2 (0.7)	0.2
Hospitalization for cardiac reasons	24 (7.7)	17 (5.6)	0.2
Acute coronary syndrome	3 (1.0)	0 (0)	0.1
Percutaneous coronary intervention	2 (0.6)	2 (0.7)	0.9
Other	19 (6.1)	15 (5.0)	0.5
Hospitalization for noncardiac surgery	35 (11.3)	39 (12.9)	0.5
Hospitalization for transient ischemic attack	0 (0)	2 (0.7)	0.1
Hospitalization for infection	22 (7.1)	24 (7.9)	0.6
Hospitalization for other noncardiac reasons	11 (3.5)	13 (4.3)	0.6
Adverse events of rate control drugs	62 (19.9)	72 (23.8)	0.2
Dizziness	9 (2.9)	16 (5.3)	0.1
Fatigue	5 (1.6)	9 (3.0)	0.1
Dyspnea	11 (3.5)	11 (3.6)	0.9
Other	42 (13.5)	40 (13.2)	0.9

Why was lenient rate control not associated with more cardiovascular morbidity and mortality? First, the incidence of heart failure was similar between the two groups. A major concern with lenient rate control is the induction or worsening of heart failure.[12-15] This concern was not confirmed by our observations. Apparently, a resting heart rate below 110 beats per minute was low enough to prevent an increased number of hospitalizations for heart failure. This observation is consistent with the notion that beta-blockers do not improve the prognosis of patients with heart failure with atrial fibrillation.[16,17]

Second, the incidence of death from cardiovascular causes was similar between the two groups. Approximately half the deaths in our study were of vascular origin, rather than arrhythmia or heart failure. Third, the rate of adverse effects of drugs, syncope, and pacemaker implantation was similar between the two groups. This observation is inconsistent with data from the AFFIRM trial.[5,11] In that trial, the rate of pacemaker implantation was 7.3% over 3.5 years, as compared with 1.4% over 3 years in the strict-control group in our trial. Reasons for this discrepancy may be that we administered rate-control drugs rather gradually. Alternatively, the thresholds for pacemaker implantation may have varied.

Finally, we did not find significant differences in the prevalence of symptoms associated with atrial fibrillation. Almost 60% of the patients in both groups were

Table 5. Incidence of primary outcome according to heart rate at the end of dose-adjustment phase

	Primary outcome	Lenient rate control	Strict rate control
Total group	13.9 (81 of 614)	12.9 (38 of 311)	14.9 (43 of 303)
Heart rate <70 beats/min	21.6 (14 of 68)	- (1 of 1)	20.4 (13 of 67)
Heart rate 70-80 beats/min	12.0 (19 of 166)	20.0 (1 of 5)	11.7 (18 of 161)
Heart rate 81-90 beats/min	13.9 (20 of 151)	15.0 (16 of 112)	10.7 (4 of 39)
Heart rate 91-100 beats/min	8.6 (12 of 143)	9.1 (11 of 123)	5.6 (1 of 20)
Heart rate >100 beats/min	19.9 (16 of 86)	14.1 (9 of 70)	46.4 (7 of 16)

symptomatic at baseline; this fraction decreased to 46% by the end of the follow-up period, a decline that may be related to underlying disease rather than to the heart rate driving symptoms.[18] Although the prevalence of symptoms was similar in the two groups in our study, we cannot rule out potential differences in the severity of symptoms between the groups. We included physically active patients, rather than sedentary patients, in our trial, because we chose to assess rate control by means of exercise testing in the strict-control group. Thus, we excluded patients with a previous stroke, resulting in a low-risk study population. These choices may have resulted in the lower-than-expected primary outcome event rate. Although we increased the number of patients from 250 to more than 300 in each treatment group, the overall frequency of the primary outcome events remained relatively low.

A trial evaluating high and low resting heart rates in patients with atrial fibrillation would ideally ensure that the relevant rate targets were met in all patients. In our strict-control group, the resting and exercise targets were achieved in 67.0% of the patients, whereas in the lenient control group the target rate was virtually always reached, without much change in therapy. We cannot rule out the possibility that we would have found significant differences between the two groups had we used a more effective means of strict rate control and had we kept heart rates just below 110 beats per minute in the lenient-control group or if we had followed patients beyond 3 years. Although we enrolled relatively low-risk patients, the subgroup analysis revealed that our results also apply to higher-risk patients (i.e., those with a $CHADS_2$ score[8] of 2 or more).

Conclusion

In conclusion, as compared with strict rate control, lenient rate control was noninferior in terms of major clinical events. Furthermore, for both patients and health care providers, lenient rate control is more convenient, since fewer outpatient visits and examinations are needed.

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Rate Control in Atrial Fibrillation

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3B

Untreated atrial fibrillation is usually associated with a rapid, irregular ventricular response and is often accompanied by symptoms including palpitations, fatigue, dyspnea, and dizziness. It is widely accepted that slowing the ventricular response, both at rest and during activity, with the use of drugs that prolong the refractory period of the atrioventricular (AV) node (so-called rate-control agents) will result in an improvement in symptoms and most likely reduce the future risk of adverse cardiovascular events. The strategy of rate control is preferred by most physicians to the strategy of rhythm control as initial therapy for patients with atrial fibrillation,[1] given the failure to show that rhythm-control strategies result in lower rates of death, stroke, or hospitalizations or better quality of life in large, well-conducted, randomized clinical trials.[2]

When choosing to administer a rate-control agent to a patient, it seems reasonable to attempt to achieve ventricular rates similar to those present during sinus rhythm in patients with a similar degree of heart disease. These targets are based on the belief that lower heart rates will result in fewer symptoms, are likely to be associated with better cardiovascular function because of longer diastolic filling times and more satisfactory hemodynamics, and are associated with a lower risk of tachycardia-related cardiomyopathy. Extrapolation from epidemiologic studies showing that faster heart rates in sinus rhythm are associated with increasing mortality from cardiovascular causes, and the documented clinical and quality-of-life benefits of the "pace and ablate" approach to ventricular rate control,[3] also imply that the more closely ventricular rates during atrial fibrillation approximate those during normal sinus rhythm, the better the outcome.

These considerations have led to widely adopted guidelines for the ventricular rate targets in patients with atrial fibrillation,[4] which recommend resting heart-rate targets of less than 80 beats per minute and targets during moderate physical activity of less than 110 beats per minute. These admittedly arbitrary targets, measured with the use of electrocardiography, are based on the expectation that the benefits of more intensive rate control outweigh its disadvantages and risks.

A number of previous lines of evidence, however, suggest possible flaws in the concept of targeting heart rates to near-normal levels. First, the relation between the achieved heart rate and the quality of life or symptoms is inconsistent, and the degree of symptoms during atrial fibrillation is more strongly related to severity of the underlying cardiac disease, age, and sex than it is to heart rate itself.[5,6] In retrospective substudies of AFFIRM (the Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial[7] and the RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) trial,[8] in which patients were randomly assigned to undergo a rate-control strategy or a rhythm-control strategy, there was no evidence of a reduction in morbidity or mortality or improved quality of life in patients with "tight" versus "less tight" rate control.[6,9] In patients with heart failure, in whom the potential deleterious effects of a high ventricular rate might be particularly prominent, there is no evidence that bisoprolol, as compared with placebo, reduced the rates of death or hospitalization in a subgroup of patients who had atrial fibrillation at baseline.[10]

In this issue of the Journal, Van Gelder and colleagues report on the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) trial (ClinicalTrials.gov number, NCT00392613).[11] They have made an important contribution to our understanding of the potential benefits and risks of the current guideline-recommended approach to ventricular rate control in patients with persistent atrial fibrillation.

By means of a variety of AV nodal blocking agents, which included beta-blocker therapy in 79% and calcium-blocker therapy in 37% of patients, a resting heart rate of less than 80 beats per minute at rest was achieved in 67% of patients who were randomly assigned to this strict rate-control target. In this group, the average (±SD) heart rate measured with the use of 24-hour Holter monitoring was 78±11 beats per minute, and 88% of patients had resting heart rates of 90 beats per minute or less after the dose-adjustment phase. Conversely, in the lenient control group, in which the resting heart-rate target was less than 110 beats per minute, 98% of patients achieved this target; resting heart rates were faster than 80 beats per minute in 98% and faster than 100 beats per minute in 23%. This less stringent rate-control target was achieved with the use of lower doses of beta-blockers, and beta-blockers were required in only 65% of patients; a combination of AV nodal blockers was necessary in 30% of patients, in contrast to 69% in the strict-control group.

Although the confidence intervals around the hazard ratios for the composite primary outcome and the components of the primary outcome are wide, there is no indication that there was any clinical benefit to strict rate control with respect to the risk of death, serious adverse outcomes (including heart failure), or symptoms. It is instructive to speculate that symptomatic adverse effects of rate-control drugs could offset the potential symptomatic benefits of strict rate control, given the minority of patients in both groups (24%) who had palpitation as a recorded symptom. In the strict-control group, the reason the target was not achieved was because of drug-related adverse events in 25% of patients. These results suggest that the potential clinical benefits of a "conventional" approach to ventricular rate control, even if present, may be offset by the potential adverse effects of drugs used for this purpose.

A number of limitations of the RACE II study need to be borne in mind. First, it is possible that rapid ventricular rates may take many years to result in cardiac deterioration and illness or death, and thus there may be a benefit of more "strict" ventricular rate control over a period of decades or more. Patients with atrial fibrillation who also have very rapid ventricular responses, present with heart failure, and appear to have tachycardia-related cardiomyopathy may have particular benefit from strict rate control; this subgroup may have been underrepresented or not enrolled in the RACE II trial. The data on symptoms and quality of life collected in the study were somewhat limited, such that subtle benefits in this regard from stricter rate control may not have been easily ascertained. As in all randomized, clinical trials, selection bias most likely limited the enrollment of patients to those who were relatively clinically well, were somewhat younger than the average age for patients with atrial fibrillation, and had some degree of rate control at study entry (mean heart rate in both groups at baseline, 96 beats per minute). Two thirds of the patients were men; women are

known to have more severe symptoms than men during atrial fibrillation, possibly in association with more rapid ventricular rates on average.[12]

What clinical inferences can be drawn from the RACE II study, given the previous state of knowledge regarding rate control? First, a heartrate target of less than 110 beats per minute at rest, although it may make physicians feel uncomfortable, is probably as useful as the current guideline-recommended target heart rates at rest and during exercise, at least in the medium term. Many patients will continue to be symptomatic under the rate-control approach, whether a strict or more lenient target heart rate is used. The RACE II study does not suggest that ventricular rate control is not needed, only that the conventional therapeutic target needs to be reassessed. At a minimum, the study indicates that reflexive, "recipe-based" adherence to a rate-control target does not seem sensible and that an approach emphasizing the adjustment of therapy on the basis of symptoms and general well-being can be safely recommended.

As in many other clinical situations, in patients with atrial fibrillation, treating a laboratory test is not a good substitute for targeting overt clinical outcomes. This important study serves as a reminder that it is better to treat the patient and not the electrocardiogram.

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4

Rate Control Efficacy in Permanent Atrial Fibrillation: Successful and Failed Strict Rate Control against a Background of Lenient Rate Control Data of the RACE II study

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Abstract

Introduction

The RACE II study showed no difference in outcome between lenient and strict rate control in patients with permanent atrial fibrillation (AF). However, in the strict group not all patients achieved the predefined heart rate target. We aimed to investigate differences in outcome between patients treated with successful strict, failed strict and lenient rate control.

Methods

The primary outcome was a composite of cardiovascular morbidity and mortality. For the current analysis outcome events were analyzed from end of the dose-adjustment phase until end of follow-up (median 2.9 [interquartile range 2.4-3.0] years). 608 of 614 patients completed the dose-adjustment phase, 301 in the strict (resting heart rate <80 beats per minute [bpm] and during moderate exercise <110 bpm) and 307 in the lenient group (resting heart rate <110 bpm). In the strict group, 203 of 301 patients achieved the rate control target, 98 failed.

Results

Heart rate was different after the dose-adjustment phase between the successful strict (72±7 bpm), failed strict (86±14 bpm), and lenient (93±8 bpm) group ($p<0.001$), and remained significantly different during follow up. The primary outcome was reached in 27 of 203 (14.2% KM estimates) in the successful strict versus 14 of 98 (15.0%) in the failed strict versus 35 of 307 (12.1%) in the lenient group ($p=0.5$). The components of the primary outcome and quality of life were similar in the groups.

Conclusion

In patients with permanent AF, successful strict rate control does not improve outcome. Lenient rate control may therefore be frontline therapy.

Introduction

Rate control is frontline therapy in patients with permanent atrial fibrillation (AF).[1,2] Evidence is accumulating that lenient rate control is a reasonable strategy in patients with permanent AF. Post-hoc analyses of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and RAte Control versus Electrical cardioversion (RACE) study showed a comparable outcome between patients with permanent AF with higher and lower heart rates.[3-5] The RAte Control Efficacy in permanent atrial fibrillation II (RACE II) trial prospectively evaluated the effect of lenient versus strict rate control in patients with permanent AF,[6] and showed no difference in outcome between the lenient and strict rate control groups in terms of cardiovascular morbidity, mortality, and quality of life.[7,8] However, not all patients achieved the heart rate target, especially not in the strict group.[7] The inability of achieving the strict rate control target may have influenced outcome, in favor of lenient rate control. The current post-hoc analysis evaluates the difference in outcome between patients treated with successful strict, failed strict and lenient rate control.

Methods

RACE II study design

The study design and results of the RACE II have been published previously.[6,7] The study was approved by the institutional review boards of all participating centers, and all patients gave written informed consent. Patients were randomized to lenient (resting heart rate <110 beats per minute [bpm]) or strict rate control (resting heart rate <80 bpm, and a heart rate <110 bpm during moderate exercise). The primary outcome was a composite of cardiovascular morbidity and mortality

Figure 1. Study flow-chart, randomization and success of rate control

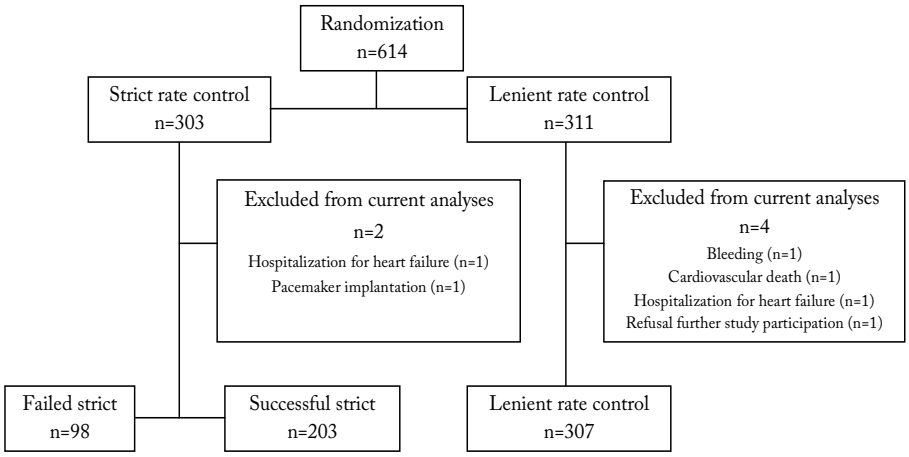


Table 1. Rate control targets and drug therapy at the end of the dose-adjustment phase

	Successful strict rate control (n=203)	Failed strict rate control (n=98)	Lenient rate control (n=307)	P Value
Rate-control target or targets achieved	203 (100)	0 (0)	302 (98.4)	
Heart rate at the end of the dose-adjustment phase – beats/min	72±7	86±14	93±8	<0.001
Resting heart rate distribution at the end of the dose-adjustment phase				
<70 beats/min	61 (30.0)	6 (6.1)	1 (0.3)	<0.001
70-80 beats/min	142 (70.0)	19 (19.4)	5 (1.6)	
81-90 beats/min	0	38 (38.8)	111 (36.2)	
91-100 beats/min	0	20 (20.4)	122 (39.7)	
>100 beats/min	0	15 (15.3)	68 (22.2)	
Resting heart rate target achieved	203 (100)	25 (25.5)	302 (98.4)	<0.001
Exercise heart rate target achieved	192 (94.6)*	27 (27.6)	-	<0.001
Mean heart rate	94±12	112±16	-	<0.001
Mean duration of exercise with target achieved – sec	90±42	103±47	-	0.049
Holter monitoring				
Mean heart rate	76±10	82±13	-	<0.001
Max RR interval – sec	2.3±0.5	2.3±0.6	-	0.9
Visits to achieve rate-control target(s)	424	255	74	<0.001
Median (interquartile range)	2 (1-3)	2 (1-3)	0 (0-0)	<0.001
Reason for failure to achieve rate-control target or targets				<0.001
Drug related adverse events	0/0	25/98	0/4	
No symptoms or symptoms tolerated	0/0	52/98	4/4	
Target impossible to achieve with drugs	0/0	21/98	0/4	

* not all patients performed exercise test due to unexpected physical limitations, eg. recent surgery (n=9)

as described previously.[7] Patients in the strict group who failed one of the heart rate criteria were classified as failed strict, the remaining patients were classified as successful strict rate control. Reasons for failure of strict rate control could be drug related adverse events, no or tolerable symptoms, or heart rate target unattainable with drugs.

Table 1. Rate control targets and drug therapy at the end of the dose-adjustment phase (continued)

	Successful strict rate control (n=203)	Failed strict rate control (n=98)	Lenient rate control (n=307)	P Value
Rate control medications in use at the end of the dose-adjustment phase – no. (%)				
No rate control drugs	1 (0.5)	2 (2.0)	32 (10.4)	<0.001
Beta-blocker alone	41 (20.2)	20 (20.4)	131 (42.7)	<0.001
Verapamil/diltiazem alone	10 (4.9)	6 (6.1)	18 (5.9)	0.9
Digoxin alone	4 (2.0)	1 (1.0)	21 (6.8)	0.015
Beta-blocker + verapamil/diltiazem	27 (13.3)	11 (11.2)	12 (3.9)	0.001
Beta-blocker + digoxin	74 (36.5)	38 (38.8)	59 (19.2)	<0.001
Verapamil/diltiazem + digoxin	21 (10.3)	8 (8.2)	16 (5.2)	0.1
Beta-blocker + verapamil/diltiazem + digoxin	18 (8.9)	8 (8.2)	3 (1.0)	<0.001
Dose at the end of the dose-adjustment phase – mg				
Betablocker (adjusted to metoprolol)	161±81	165±95	121±78	<0.001
Verapamil	212±94	233±102	168±60	0.004
Diltiazem	225±50	207±90	230±87	0.9
Digoxin	0.19±0.07	0.23±0.1	0.19±0.08	0.007

Design of current analysis

For the current analysis outcome events in the strict rate control group were analyzed from end of the dose-adjustment phase, i.e. the moment the heart rate targets were either achieved or deemed impossible or unnecessary (due to absence of complaints) to achieve, until end of follow-up. In the lenient rate control group the endpoints were analyzed from 9 days after randomization, the mean duration of the dose-adjustment phase in the lenient group, until end of follow-up. Patients with a primary outcome event occurring during the dose-adjustment phase in the strict group and before 9 days after randomization in the lenient group were not included in the present analysis.

Quality of life

Quality of life was assessed with the Medical Outcome Study Short Form-36, AF severity scale, and Multidimensional Fatigue Inventory-20 as has been described previously.[8-12]

Table 2. Baseline characteristics at randomization

	Successful strict rate control (n=203)	Failed strict rate control (n=98)	Lenient rate control (n=307)	P Value
Age – yr	68±8	66±9	68±8	0.1
Male sex – no. (%)	129 (63.6)	67 (68.4)	201 (65.8)	0.7
Total atrial fibrillation duration (months)	21 (6-59)	19 (5-68)	16 (6-54)	0.1
Duration permanent atrial fibrillation (months)	3 (1-7)	2 (1-5)	3 (1-6)	0.2
Hypertension – no. (%)	120 (59.1)	54 (55.1)	197 (64.2)	0.4
Coronary artery disease – no. (%)	34 (16.8)	10 (10.2)	65 (21.2)	0.1
Valvular heart disease – no. (%)	42 (20.7)	18 (18.4)	63 (20.5)	0.9
Chronic obstructive pulmonary disease – no. (%)	33 (16.3)	10 (10.2)	35 (11.4)	0.3
Diabetes mellitus – no. (%)	20 (9.9)	12 (12.2)	36 (11.7)	0.7
Lone atrial fibrillation* – no. (%)	3 (1.5)	3 (3.1)	5 (1.6)	0.8
Previous heart failure hospitalization – no. (%)	25 (12.3)	7 (7.1)	28 (9.1)	0.4
$CHADS_2$ score†	1.4±1.2	1.4±1.1	1.4±1.0	0.9
0 or 1 – no. (%)	130 (64.0)	64 (65.3)	176 (57.3)	0.3
2 – no. (%)	44 (21.7)	20 (20.4)	93 (30.3)	
3-6 – no. (%)	29 (14.3)	14 (14.3)	38 (12.4)	
Symptoms – no. (%)	119 (58.6)	55 (56.1)	169 (55.1)	0.5
Palpitations	60 (29.6)	22 (22.5)	61 (19.9)	0.1
Dyspnea	80 (39.4)	29 (29.6)	101 (32.9)	0.04
Fatigue	67 (33.0)	29 (29.6)	85 (27.7)	0.6
New York Heart Association functional class				
I – no. (%)	123 (60.6)	69 (70.4)	206 (67.1)	0.1
II – no. (%)	69 (34.0)	27 (27.6)	85 (27.7)	
III – no. (%)	11 (5.4)	2 (2.0)	16 (5.2)	
Body-mass index	29±5	29±4	29±5	0.7
Blood pressure				
Systolic	135±17	135±15	137±19	0.4
Diastolic	82±12	83±9	85±11	0.02
Heart rate in rest – beats/minute	94±11	98±15	96±12	0.1

* Lone atrial fibrillation was defined as AF in the absence of cardiovascular disease and extracardiac precipitating causes of AF

† The CHADS2 score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicate a greater risk. Congestive heart failure, hypetension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all points for a given patient.

Table 2. Baseline characteristics at randomization (continued)

	Successful strict rate control (n=203)	Failed strict rate control (n=98)	Lenient rate control (n=307)	P Value
Echocardiography parameters – mm				
Left atrial size, long axis	46±7	46±8	46±6	0.6
Left atrial volume - mL	72±28	76±26	72±24	0.3
Left ventricular end-diastolic diameter	51±8	52±8	51±7	0.8
Left ventricular end-systolic diameter	36±8	37±9	36±8	0.8
Left ventricular ejection fraction – %	52±12	53±13	52±11	0.6
≤ 40% – no. (%)	34 (16.7)	14 (14.3)	43 (15.6)	0.4
Rate control medications in use – no. (%)				
No rate control drugs	20 (9.9)	7 (7.1)	36 (11.7)	0.5
Beta-blocker alone	93 (45.8)	42 (42.9)	139 (45.3)	0.9
Verapamil/diltiazem alone	13 (6.4)	6 (6.1)	17 (5.5)	0.7
Digoxin alone	15 (7.4)	9 (9.2)	19 (6.2)	0.6
Beta-blocker + verapamil/diltiazem	7 (3.5)	4 (4.1)	7 (2.3)	0.8
Beta-blocker + digoxin	26 (12.8)	22 (22.5)	53 (17.3)	0.2
Verapamil/diltiazem + digoxin	11 (5.4)	3 (3.1)	14 (4.6)	0.8
Beta-blocker + verapamil/diltiazem + digoxin	5 (2.5)	0 (0.0)	2 (0.7)	0.2
Sotalol or amiodarone	13 (6.4)	5 (5.1)	20 (6.5)	0.2
Dose – mg				
Betablocker (adjusted to metoprolol)	124±65	115±67	114±71	0.6
Verapamil	180±72	215±79	173±77	0.3
Diltiazem	233±58	160±57	230±87	0.7
Digoxin	0.17±0.06	0.22±0.06	0.19±0.08	0.1
Other medications in use – no. (%)				
ACE inhibitor and/ or ARB	94 (46.3)	45 (45.9)	165 (53.8)	0.2
Diuretic	78 (38.4)	35 (35.7)	134 (43.7)	0.1
Statin‡	54 (26.6)	20 (20.4)	101 (32.9)	0.1
Vitamin K antagonist	200 (98.5)	96 (98.0)	304 (99.0)	0.9
Aspirin	4 (2.0)	2 (2.0)	4 (1.3)	0.9

ACE – angiotensin converting enzyme inhibitor, ARB – angiotensin II receptor blocker
‡ statins were defined as 3-hydroxy-3-methylglutaryl-coenzym A reductase inhibitors

Statistical analysis

Baseline descriptive statistics are presented as mean ± standard deviation (SD) or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, in terms of patient characteristics, were evaluated by one-way ANOVA, Kruskal-Wallis test or Chi-square test, depending on normality and type of the data. Differences in quality of life between the groups were assessed with a general linear model and a general linear model repeated measures. In all analyses a value of $p<0.05$ was considered statistically significant. Kaplan-Meier analysis was performed to assess differences in outcome between the three groups. Non-inferiority was tested by comparing the upper boundary of the 90% confidence interval (CI) for the primary outcome.[7]

Results

Rate control achievement during the dose adjustment phase

In the current analysis 608 patients were included. 203 patients had successful strict, 98 failed strict, and 307 patients lenient rate control (Figure 1). In 25 patients strict rate control failed due to drug related adverse events, 52 patients had no or tolerable symptoms, and in 21 patients the strict heart rate criteria were unattainable to achieve with drugs.

Patient characteristics

Heart rates were higher in the failed strict and lenient group as compared to the successful strict group (Table 1).

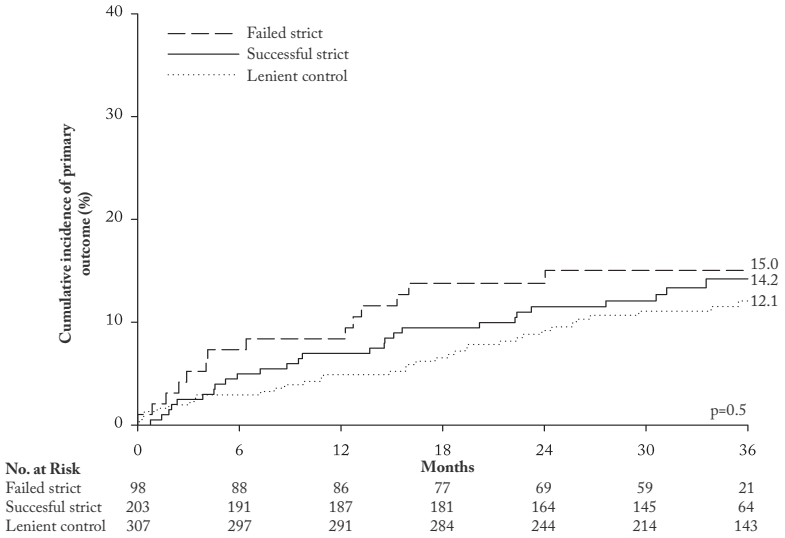
Median follow up was 2.9 (interquartile range 2.4-3.0) years. Clinical characteristics were almost comparable between the groups (Table 2).

After the dose-adjustment phase, more patients in the lenient group either used no rate control drugs, or a beta-blocker or digoxin alone. Fewer patients in the lenient group used a combination of drugs and used significantly lower dosages of beta-blockers and verapamil (Table 1).

Primary outcome after dose-adjustment phase

A total of 76 patients (27 of 203 in the successful strict and 14 of 98 in the failed strict group, and 35 of 307 in the lenient group) reached the primary outcome (Figure 2, Table 3A and B). The cumulative difference between successful strict and failed strict was -0.8 (90% CI -6.6 to 8.2, p for non-inferiority 0.02). The cumulative difference between successful strict and lenient rate control was 0.2, 90% CI -7.4 to 3.2, p for non-inferiority <0.001). There was no significant difference between the three groups considering the composites of the primary outcome, nor was there any difference in all cause mortality (Table 3). There was also no difference in primary outcome when analyzing patients with an ejection fraction <40% (data not shown, p=0.6).

Figure 2. Kaplan-Meier estimates of the cumulative incidence of the primary outcome



No. at Risk							
Failed strict	98	88	86	77	69	59	21
Succesful strict	203	191	187	181	164	145	64
Lenient control	307	297	291	284	244	214	143

Additional visits, heart rate, left ventricular function and drug use during study

At 1 and 2 years follow-up more patients in the successful strict (17.7% and 12.3%) and failed strict (14.3% and 8.2%), as compared to the lenient (4.6% and 4.2%) group had at least one additional visit ($p<0.001$ and $p=0.007$ for 1 and 2 years of follow-up, respectively). There was no difference in additional visits between the successful strict and failed strict groups.

Heart rates during the study and left ventricular ejection fraction during the study are shown in Table 4. During follow-up no significant changes in drug or combination of drugs occurred in any of the groups, nor were there significant changes in the dosages of the rate control drugs (data not shown).

Symptoms and quality of life

At the end of study fewer patients in the failed strict group had any symptom of AF (Table 5). At study entry nor at study end, there were no significant differences in the SF-36, MFI-20, and AF-severity scale between the groups (Figure 3). There was no effect of the different rate control strategies over time.

Discussion

This analysis of RACE II shows no difference in cardiovascular outcome between successful strict, failed strict and lenient rate control in patients with permanent AF. In addition, quality of life was comparable between the groups at the end of follow-up.

Table 3A. Cumulative Incidence* of the Composite Primary Outcome and its Components†

	Successful strict rate control (n=203)	Failed strict rate control (n=98)	Lenient rate control (n=307)
Primary Outcome	No. of patients (%)‡		
Composite primary outcome	27 (14.2)	14 (15.0)	35 (12.1)
Death from cardiovascular cause	5 (2.7)	6 (6.7)	7 (2.3)
Cardiac arrhythmic death	1 (0.5)	3 (3.2)	2 (0.7)
Cardiac nonarrhythmic death	0	2 (2.5)	1 (0.3)
Noncardiac vascular death	4 (2.2)	1 (1.1)	4 (1.3)
Heart failure	5 (2.9)	5 (5.8)	10 (3.5)
Stroke	8 (4.2)	3 (3.2)	4 (1.6)
Ischemic stroke	7 (3.7)	1 (1.1)	3 (1.3)
Hemorrhagic stroke	2 (1.2)	2 (2.2)	1 (0.3)
Systemic embolism	0	0	1 (0.3)
Bleeding	9 (4.5)	4 (4.6)	14 (5.0)
Intracranial bleeding	2 (1.0)	1 (1.1)	0
Extracranial bleeding	7 (3.5)	3 (3.5)	14 (5.0)
Syncope	2 (1.0)	1 (1.1)	3 (1.0)
Life threatening adverse effects of rate control drugs	1 (0.5)	1 (1.0)	3 (1.0)
Sustained ventricular tachycardia or ventricular fibrillation	1 (0.5)	0	0
Implantable cardioverter defibrillation implantation	1 (0.6)	0	0
Pacemaker implantation	1 (0.6)	2 (2.1)	2 (0.8)
Death from any cause§	10 (5.6)	8 (8.9)	15 (5.0)

* Composite primary outcome includes first event for each patient, component events include all such events.
† Outcome event in the successful strict and failed strict rate control were analyzed from the end of the dose-adjustment phase until end of study. In the lenient rate control group the outcome event were analyzed from 9 days, the mean duration of the dose-titration in the lenient rate control group, until the end of follow-up.
‡ The cumulative incidence at 3 years of follow-up was determined with use of the Kaplan-Meier curves.
§ Death from any cause is not a composite of the primary outcome
CI – confidence interval

One of the comments on the RACE II study is that only 67% of the patients randomized to the strict group achieved the heart rate targets, as compared to 98% in the lenient group. The data of the present analysis confirm our prior findings that lenient rate control is not inferior to strict rate control, even not when the lenient strategy is compared to patients who were successfully treated with a strict rate control

Table 3B. Hazard Ratio of the Composite Primary Outcome and its Components

	Hazard Ratio (95% Confidence Interval)		
	Failed strict versus successful strict	Successful strict versus lenient	Failed strict versus lenient
Composite primary outcome	1.17 (0.62-2.24)	1.23 (0.74-2.03)	1.44 (0.78-2.69)
Death from cardiovascular cause	2.66 (0.81-8.73)	1.08 (0.34-3.39)	2.86 (0.96-8.54)
Heart failure	2.24 (0.65-7.73)	0.74 (0.25-2.18)	1.67 (0.57-4.88)
Stroke	0.83 (0.22-3.14)	3.01 (0.91-10.02)	2.51 (0.56-11.23)
Bleeding	0.97 (0.30-3.16)	0.97 (0.42-2.25)	0.95 (0.31-2.88)

strategy.[1,2,7,13,14] Instead, the present analysis shows that attempts to achieve strict rate control targets are unsuccessful in one third of the patients and not necessary. The latter may not hold for every patient. If patients remain symptomatic or a tachycardiomyopathy develops lower hear rate targets may be indicated.

In accordance with AFFIRM, we also showed that a strict rate control strategy is time consuming, necessitating more out-patient visits, more combinations

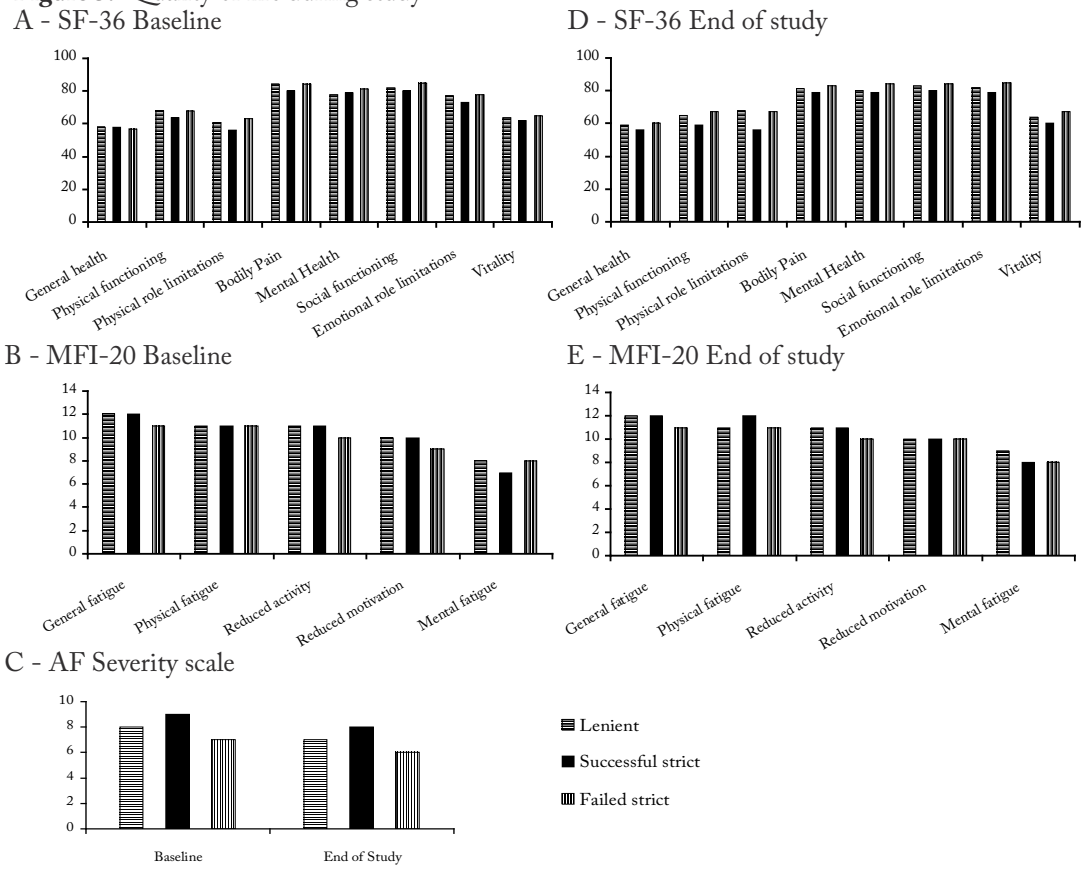
Table 4. Heart rate during follow-up and left ventricular ejection fraction at end of study

	Successful strict rate control	Failed strict rate control	Lenient rate control	P Value
Heart rate				
1 year	73±10	81±14	85±13	<0.001
2 year	74±12	78±12	83±13	<0.001
End of study	75±14	78±12	85±13	<0.001
Left ventricular ejection fraction at end of study	55±11	55±9	54±11	0.4

Table 5. Symptoms of AF at end of study

	Successful strict rate control (n=189)	Failed strict rate control (n=83)	Lenient rate control (n=282)	P Value
Symptoms – no. (%)	97 (51.3)	29 (34.9)	129 (45.7)	0.03
Palpitations	18 (9.5)	8 (9.6)	30 (10.6)	0.9
Dyspnea	62 (32.8)	19 (22.9)	85 (30.1)	0.3
Fatigue	45 (23.8)	17 (20.5)	69 (24.5)	0.7

Figure 3. Quality of life during study



and higher dosages of rate control drugs.[3,7,15] These differences emphasize the difference in strategy. Although the dissimilarity in heart rates between the groups was not as marked as may have been anticipated, strategies to obtain those heart rates were completely different.

Why was successful strict rate control not associated with an improved outcome? First, the incidence of heart failure, being a major concern of lenient rate control, was not lower during successful strict rate control. Apparently, a heart rate <110 bpm was low enough to prevent heart failure, being in line with post-hoc analyses of large heart failure trials showing that beta-blockers do not improve outcome in patients with heart failure and AF.[16-18] Secondly, patients with AF may need higher heart rates due to loss of the atrial kick and the irregular ventricular response.[19]

There were no differences in quality of life between the three rate control groups. Apparently, not heart rate alone but also the use of more and higher dosages of rate control drugs and the underlying disease influence quality of life.

Limitations

The difference in heart rate between the groups was not as marked as would have been expected from the design of the study. However, the strategies to achieve those heart rates were completely different. Outcome might have been different when all patients in the lenient group would have had a heart rate >100 bpm.[13] RACE II was not designed to assess differences between successful strict, failed strict and lenient rate control, therefore the current study is underpowered for this analysis. Follow up was limited to 3 years.

Conclusion

There is no difference in outcome between successful and failed strict rate control. Strict rate control seems to have no favorable effect in this group of permanent AF patients, even not when the heart rate targets are achieved. Lenient rate control, therefore, may be used as frontline therapy in patients with permanent AF.

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The Effect of Rate Control on Quality of Life in Patients with Permanent Atrial Fibrillation Data of the RACE II study

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Abstract

Introduction

The RAte Control Efficacy in permanent atrial fibrillation II (RACE II) trial showed that lenient rate control is not inferior to strict rate control in terms of cardiovascular morbidity and mortality. The influence of rate control on quality of life (QoL) is unknown. We hypothesized that QoL is comparable between patients randomized to lenient versus strict rate control.

Methods

In RACE II 614 patients with permanent atrial fibrillation (AF) were randomized to lenient (resting heart rate [HR]<110 bpm) or strict rate control (resting HR<80 bpm, HR during moderate exercise <110 bpm). QoL was assessed in 437 patients using the Short Form (SF)-36 health survey questionnaire, AF severity scale, and Multidimensional Fatigue Inventory (MFI)-20, at baseline, 1 year and end of study. QoL changes were related to patient characteristics.

Results

Median follow-up was 3 years. Mean age was 68±8 years, 66% were males. At the end of follow-up all SF-36 subscales were comparable between both groups. The AF severity scale was similar at baseline and end of study. At baseline and at end of study there were no differences in the MFI-20 subscales between the two groups. Symptoms at baseline, younger age, and less severe underlying heart disease, rather than assigned therapy or heart rate, were associated with QoL improvements. Female sex and cardiovascular endpoints during the study were associated with worsening of QoL.

Conclusion

Stringency of heart rate control does not influence quality of life. Instead, symptoms, gender, age and severity of the underlying heart disease influence QoL.

Introduction

Atrial fibrillation (AF) causes symptoms like palpitations, dyspnea and fatigue.[1] Compared to healthy subjects, quality of life is reduced in patients with AF.[2,3] Restoration and maintenance of sinus rhythm improves quality of life,[3-6] but sinus rhythm can be maintained in a minority of patients.[7-9] The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trials showed no improvement in cardiovascular morbidity and mortality and quality of life during a rhythm control strategy.[7,8] Therefore rate control has become first choice therapy in elderly patients without severe symptoms. The optimal level of heart rate control, however, was unknown. Recently the Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II (RACE II) showed that lenient rate control is as effective as strict rate control with respect to morbidity and mortality.[10] Strict rate control may improve quality of life due to a reduction of the heart rate. On the other hand, more negative dromotropic drugs and higher doses may reduce this positive effect on quality of life.

We hypothesized that quality of life is comparable between lenient and strict rate control. The aim of this predefined substudy of the RACE II trial was to assess the effect of stringency of heart rate control on quality of life measured with a general health, AF specific and fatigue questionnaire.[11] In addition, we investigated patient characteristics associated with a low quality of life at baseline and changes in quality of life during follow-up.

Methods

Patient population

This study was performed in patients with permanent AF included in the RACE II study.[10,11] The institutional review board of each participating hospital approved the study, and all patients gave written informed consent. We included 614 patients who were randomized to lenient rate control (resting heart rate <110 beats/min) or strict rate control (resting heart rate <80 beats/min, and heart rate <110 beats/min during moderate exercise). Rate control was instituted with beta-blockers, non-dihydropyridine calcium-channel blockers, and digoxin, alone or in combination and at various doses, until the heart rate target was achieved.[11] Drug use at the end of the dose-adjustment phase was used as baseline medication in the current analysis. The primary outcome in the main study was a composite of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation. The arrhythmic events were analyzed for the purpose of the present substudy as the occurrence of any composite arrhythmic endpoint. Both strategies were associated with a comparable rate of cardiovascular adverse events.

Table 1. Baseline characteristics

	Lenient rate control (n=230)	Strict rate control (n=207)	Total population (n=437)
Age – yr	69±7	68±8	68±8
Male sex – no. (%)	157 (68.3)	133 (64.3)	290 (66.4)
Total atrial fibrillation duration (months)	17 (6 – 54)	19 (6 – 58)	18 (6 – 58)
Duration permanent atrial fibrillation (months)	3 (1-6)	3 (1-5)	3 (1-6)
Heart rate in rest – beats per minute	95±14	95±11	95±12
Hypertension – no. (%)	144 (62.6)	120 (58.0)	264 (60.4)
Coronary artery disease – no. (%)	53 (23.0)	30 (14.5)*	83 (19.0)
Valvular heart disease – no. (%)	44 (19.1)	45 (21.7)	89 (20.4)
Chronic obstructive pulmonary disease – no. (%)	25 (11.6)	26 (14.2)	51(12.9)
Diabetes mellitus – no. (%)	21 (9.1)	19 (9.2)	40 (9.2)
Lone atrial fibrillation† – no. (%)	5 (2.2)	6 (2.9)	11 (2.5)
Previous heart failure hospitalization – no. (%)	19 (8.3)	18 (8.7)	37 (8.5)
$CHADS_2$ score‡ – no. (%)	1.3±1.0	1.3±1.1	1.3±1.0
0 or 1	143 (62.2)	139 (67.1)	282 (64.5)
2	64 (27.8)	43 (20.8)	107 (24.5)
3-6	23 (10.0)	25 (12.1)	48 (11.0)
Symptoms – no. (%)	127 (61.4)	127 (55.2)	254 (58.1)
Palpitations	47 (20.4)	59 (28.5)*	106 (24.3)
Dyspnea	77 (33.5)	84 (40.6)	161 (36.8)
Fatigue	65 (28.3)	69 (33.3)	134 (30.7)
New York Heart Association functional class			
I – no. (%)	153 (66.5)	124 (59.9)	277 (63.4)
II – no. (%)	64 (27.8)	75 (36.2)	139 (31.8)
III – no. (%)	13 (5.7)	8 (3.9)	21 (4.8)
Echocardiographic parameters – mm			
Left atrial size, long axis	46±7	46±7	46±7
Left ventricular end-diastolic diameter	51±7	51±7	51±7
Left ventricular end-systolic diameter	36±8	36±9	36±8
Left ventricular ejection fraction – %	52±11	53±12	53±11
≤ 40% – no. (%)	28 (12.2)	32 (15.5)	60 (13.7)

† Lone atrial fibrillation was defined as AF in the absence of cardiovascular disease and extracardiac precipitating causes of AF

‡ The $CHADS_2$ score is a measure of the risk of stroke in patients with atrial fibrillation, with scores ranging from 0 to 6 and higher scores indicate a greater risk. Congestive heart failure, hypetension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all points for a given patient.

NYHA - New York Heart Association functional class for heart failure

Table 1. Baseline characteristics (continued)

	Lenient rate control (n=230)	Strict rate control (n=207)	Total population (n=437)
Heart rate distribution at the end of the dose adjustment phase			
< 70 beats per minute – no.(%)	1 (0.4)	45 (21.7)	<0.001
70 to 80 beats per minute – no.(%)	4 (1.8)	119 (57.5)	<0.001
81 to 90 beats per minute – no.(%)	81 (35.2)	24 (11.6)	<0.001
91 to 100 beats per minute – no.(%)	93 (40.4)	11 (5.3)	<0.001
>100 beats per minute – no.(%)	51 (22.2)	8 (3.9)	<0.001
Rate control medications use at the end of the dose-adjustment phase – no. (%)			
No rate control drugs	24 (10.4)	2 (1.0)	26 (6.0)
Beta-blocker alone	99 (43.0)	46 (22.2)	145 (33.2)
Verapamil/diltiazem alone	13 (5.7)	11 (5.3)	24 (5.5)
Digoxin alone	18 (7.8)	1 (0.5)	19 (4.4)
Beta-blocker + verapamil/diltiazem	7 (3.0)	25 (12.1)	32 (7.3)
Beta-blocker + digoxin	45 (19.6)	79 (38.2)	124 (28.4)
Verapamil/diltiazem + digoxin	13 (5.7)	24 (11.6)	37 (8.5)
Beta-blocker + verapamil/diltiazem + digoxin	1 (0.4)	14 (6.8)	15 (3.4)
Sotalol or amiodaron	10 (4.4)	5 (2.4)	15 (3.4)
Dose – mg (no. of patients)			
Beta-blocker (normalized to metoprolol-equivalent doses)	119±81 (153)	169±87 (166)	145±88 (319)
Verapamil	183±56 (30)	221±102 (69)	209±92 (99)
Diltiazem	230±87 (4)	233±52 (6)	232 ±63 (10)
Digoxin	0.19±0.8 (82)	0.21±0.9 (120)	197 ±83 (202)
Other medications in use at the end of the dose-adjustment phase – no. (%)			
ARB or ACE inhibitor	122 (53.0)	100 (48.3)	222 (50.8)
Diuretic	98 (42.6)	81 (39.1)	179 (41.0)
Statin§	82 (35.7)	51 (24.6)*	133 (30.4)
Vitamin K antagonist	228 (99.1)	203 (98.1)	431 (98.6)
Aspirin	2 (0.9)	4 (1.9)	6 (1.4)

§ Statins were defined as 3-hydroxy-3-methylglutaryl-coenzym A reductase inhibitors
ACE inhibitor – Angiotensin-converting enzyme inhibitor, ARB – Angiotensin receptor blocker

Patients were excluded from the present analyses when they did not complete one of the quality of life questionnaires during follow-up (64 patients in the lenient and 78 patients in the strict-control arm). Patients who died during the study were also not included in the analysis (17 patients in the lenient and 18 in the strict-control group). Minimum follow-up was 2 years, maximal follow-up 3 years. Median follow-up was 3 years (interquartile range [IQR] 2.2-3.1 years). Results of the questionnaires at baseline, 12 months and end of study are presented. Importantly, the 12 months follow-up was the first measurement of quality of life after the dose-adjustment phase.

Baseline characteristics were comparable between the excluded patients and included patients. Baseline characteristics of the included patients are shown in Table 1. With the exception of a higher prevalence of coronary artery disease and use of statins in the lenient group, baseline characteristics were comparable between both groups. After the dose adjustment phase 98% of the patients in the lenient group met the heart rate target versus 76% in the strict control group. Patients randomized to strict rate control used more and higher dosages of negative dromotropic drugs compared to lenient rate control (Table 1). During the total follow up the heart rate was significantly higher in the lenient compared to the strict rate control group (after dose adjustment 93±8 versus 76±11 beats per minute, at 1 year 84±13 versus 74±12 beats per minute, at end of study 84±14 versus 75±14 beats per minute, all $p<0.05$).

Quality of life questionnaires

General health related quality of life was measured with The Medical Outcome Study Short Form-36 (SF-36). The SF-36 is a standardized, validated, general health survey that has been frequently used in arrhythmia studies.[12] The SF-36 has been translated and validated in the Netherlands.[13] It contains items to assess physical health (general health perception, physical functioning, role limitations due to physical problems and bodily pain) and mental health (social functioning, role limitations due to emotional problems, mental health, and vitality). The items for general health perception and vitality measure both physical and mental health. Each scale is composed of a number of multiple choice questions. For each of the eight subscales, scores are transformed to a scale ranging from 0-100, lower scores representing lower quality of life.

Severity of AF-related symptoms was assessed with the University of Toronto AF Severity Scale (AF severity scale).[2,14,15] This is a disease-specific instrument intended to measure the patient's perception of severity of arrhythmia-related symptoms. This is a seven-item questionnaire that included common AF symptoms (e.g. palpitations and dyspnea). Items are rated on a six-point scale. Scores range from 0-35, higher scores indicating greater AF symptoms severity.

Severity of fatigue was measured with the Multidimensional Fatigue Inventory-20 (MFI-20).[16,17] The MFI-20 is a self-report instrument containing 20 statements covering different aspects of fatigue. The 20 items are organized in 5 scales, general, physical and mental fatigue and reduced activity and motivation, ranging from 4-20. The scales are balanced to reduce influence of response tendencies.

Statistical analysis

To analyze patient characteristics associated with low quality of life at baseline, patients with low scores (scores lower than the mean value –1SD) were identified. To assess relevant changes over time in SF-36 subscales, the changes over time were divided into relevant and irrelevant. A relevant change was pre-defined for each SF-36 subscale. The relevant change was based on the number of steps the patient improved or worsened on the stepwise multiple choice questions that comprised each SF-36 subscale between baseline, and end of study.[3] The following changes in individual patients were regarded as relevant: one step for role limitation due to physical problems and role limitations due to emotional problems, two steps for social functioning and bodily pain, and three steps for general health perception, physical functioning, mental health, and vitality. Based on the above definition of relevant changes in the SF-36 subscales the relevant effect size of each SF-36 subscale was defined as 0.58 standard deviation (SD) or higher from baseline.[18] Also for the AF severity scale and the MFI-20 a relevant change was defined as an effect size of >0.58 SD in these questionnaires, which is in accordance with the literature which defines an effect size between 0.50 and 0.80 SD as a moderate change.[18]

Clinical correlates of change in quality of life, including clinical baseline and follow-up characteristics, were determined. The use of beta-blockers was included in this analysis, since beta-blockers effectively reduce heart rate, but may reduce exercise capacity and induce fatigue.[19] Use of other negative dromotropic drugs or a combination of negative dromotropic drugs, and dosages were not included in this analysis. This was not performed because randomization strategy was our variable of interest, not different types or combinations of negative dromotropic drugs. Furthermore, due to the high number of possible combinations of negative dromotropic drugs and dosages, this would inappropriately complicate the analysis.

To examine changes over time for each quality of life questionnaire and subsequent subscale the method of repeated measures was performed. For comparison of scores between groups a general linear model and the Student t test for independent variables was used. Variables with a non-normal distribution were tested with the Mann-Whitney and the Wilcoxon test. Correlation between heart rate and quality of life was assessed with Pearson's correlation. The univariate chi-square test and Student t test for independent variables, followed by multivariate stepwise logistic regression analyses were performed to determine predictors of relevant quality of life change over follow-up. Baseline characteristics, high baseline heart rate (>100 beats/min) in combination with a relevant (>20% heart rate reduction), occurrence of a primary endpoint and symptoms during the study were univariately tested in a logistic regression model. All univariate predictors with $p < 0.1$ were tested in a multivariate logistic regression model using a stepwise approach. In the multivariate model, a variable was excluded when $p \geq 0.05$. In all analysis a value of $p < 0.05$ was considered statistically significant. All analyses were performed on an intention to treat basis.

Table 2. SF-36 scores

SF-36 Subscale	Strategy	Baseline	12 months	End of study	Relevant improvement from baseline to end of study (%)	Relevant worsening from baseline to end of study (%)
General Health	Lenient	59 (17)	58 (18)	59 (19)	19	16
	Strict	58 (18)	59 (18)	58 (19)	16	23
Physical functioning	Lenient	70 (22)	69 (23)	65 (25) †	13	24
	Strict	64 (25)	68 (24) †	62 (27) †	17	26
Physical role limitation	Lenient	64 (42)	62 (42)	69 (41)	24	24
	Strict	58 (42)	68 (40) †	60 (44)	28	24
Bodily pain	Lenient	84 (20)	84 (22)	81 (22)†	14	21
	Strict	81 (22)	83 (21)	80 (23)	16	17
Mental Health	Lenient	79 (17)	79 (16)	79 (18)	22	18
	Strict	81 (15)	81 (14)	81 (14)	18	24
Social functioning	Lenient	84 (20)	85 (18)	84 (21)	15	13
	Strict	82 (21)	84 (21)	81 (22)	17	15
Emotional role limitation	Lenient	78 (36)	79 (36)	82 (33)	21	17
	Strict	78 (36)	81 (14)	81 (34)	22	13
Vitality	Lenient	66 (20)	65 (18)	64 (21)	17	23
	Strict	64 (19)	64 (19)	63 (20)	16	19

† p< 0.05 compared to baseline score

Results

Symptoms of AF during study

At baseline 58% of patients experienced symptoms of AF, being predominantly dyspnea, fatigue, and palpitations (Table 1). At end of study 48% of patients experienced symptoms of AF, (dyspnea in 139 [32%], fatigue in 110 [25%], and palpitations in 49 [11%] patients). There were no differences in symptoms of AF at either baseline or at end of study between the lenient and strict group (Figure 1).

Quality of life at baseline

At study entry, SF-36 scales were comparable between the lenient and strict group (Table 2). Low SF-36 subscales scores (scores below the mean value minus 1 SD) at baseline were associated with the presence of symptoms (all SF-36 subscales), diabetes mellitus (subscale general health), and female sex (subscales physical functioning, physical role limitation, bodily pain, social functioning, and vitality).

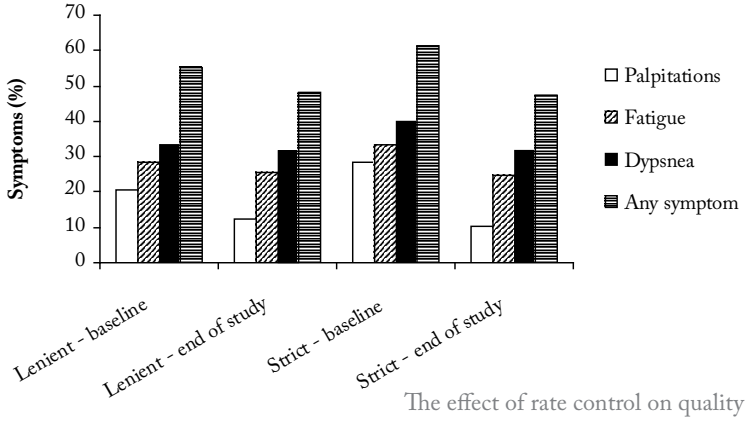
Table 3. MFI-20 scores

	Strategy	Baseline	12 months	End of study	Relevant improvement from baseline to end of study (%)	Relevant worsening from baseline to end of study (%)
General fatigue	Lenient	11±5	11±5	12±5	21	24
	Strict	11±5	11±5	12±5	19	22
Physical fatigue	Lenient	11±5	11±5	11±5	17	27
	Strict	11±5	11±5	12±5	21	25
Reduced activity	Lenient	11±5	10±4	11±4	22	24
	Strict	11±5	11±4	11±5	20	26
Reduced motivation	Lenient	10±4	9±4	10±4	20	24
	Strict	10±4	9±4	10±4	17	30
Mental fatigue	Lenient	8±4	8±4	9±4	16	26
	Strict	7±4	8±4	8±4	15	25

At baseline no significant differences between the lenient (6 [interquartile range {IQR} 3-11]) and strict (7 [IQR 3-12]) groups existed in AF severity scale. High AF severity scale scores (indicating more symptoms of AF) at baseline (scores above the mean value + 1 SD) were associated with symptoms of AF and female sex.

All subscales of the MFI 20 were comparable between both groups at baseline (Table 3). High scores (scores above the mean value + 1 SD) on the MFI-20 subscales, indicating more symptoms of fatigue, were associated with symptoms of AF at baseline (general fatigue, physical fatigue, reduced activity, reduced motivation), and female sex (physical fatigue and reduced activity). There was also no difference in quality of life, in any of the questionnaires used, between patients with a high baseline heart rate (>100 beats/min) versus a normal baseline heart rate (data not shown).

Figure 1. Percentage of patients with any symptom



Changes in quality of life from baseline to end of study

In the lenient group, no significant differences were found between baseline and 12 months follow-up in the SF-36. However, at study end the subscales physical functioning and bodily pain significantly worsened compared to baseline (Table 2). In the strict group, at 12 months of follow-up, physical functioning and role limitations due to physical problems improved (Table 2). At 12 months of follow-up and at the end of study, no differences were present between the lenient and strict rate control groups in any of the SF-36 subscales (Table 2). There were also no significant correlations between heart rate at baseline, at the end of the dose-adjustment phase nor end of study, and the SF-36 subscales scores of baseline and study end, respectively. There was also no relation with heart rate and changes in quality of life. Comparable percentages of patients showed a relevant improvement or worsening from baseline to end of study in the different subscales. All effect sizes were <0.25, indicating small changes from baseline to end of study.

There were no significant differences in AF severity scale in either the lenient (6 [IQR 3-11]) and strict (6 [IQR 3-11]) group between baseline and end of study. At the end of follow-up the AF severity scale was comparable between both groups. At baseline and at end of study no correlation was found between heart rate and the AF severity scale. The relevant changes in the AF severity scale were comparable in the lenient (improvement 22%, worsening 26%) and strict (improvement 26%, worsening 21%) group. All effect sizes (i.e. measurement of the magnitude of change over time) were 0, indicating no changes from baseline to end of study.

From baseline to 12 months of follow-up and till study end, there were no significant differences in either rate control strategy in any of the MFI subscales. There were also no differences between the lenient and strict rate control groups during total follow-up (Table 3). The MFI-20 subscales at baseline and end of study were not correlated with heart rate at baseline, at the end of the dose-adjustment phase, nor at end of study. All effect sizes were below or equal to 0.25, indicating small changes from baseline to end of study.

Determinants of changes in quality of life

We investigated whether rate control strategy, baseline characteristics and follow-up parameters were associated with relevant changes in quality of life in each questionnaire, and their subscales. The parameters considered in this analysis were underlying disease, echocardiographic parameters at baseline, change in left ventricular ejection fraction from baseline to end of study, symptoms, heart rate at the end of the dose-adjustment phase, relevant heart rate reduction of a high baseline heart rate (>100 beats/min in combination with ≥20% reduction from baseline to the end of the dose-adjustment phase), occurrence of a primary endpoint and one of the composites of the primary endpoint: hospitalization for heart failure, stroke, major bleeding, and arrhythmic events.

Table 4. Patient characteristics associated with a relevant improvement or worsening in SF-36 scores from baseline to end of study, described in odds ratio

	Determinants of change	OR (95% CI)	P Value
Improvement in SF-36			
General Health	No symptom at end of study	1.7 (1.0-3.0)	0.049
Physical functioning	-	-	-
Physical role limitation	Any symptom at baseline	2.0 (1.2-3.4)	0.013
	LVEF per 10%	1.3 (1.0-1.7)	0.021
	Septum per mm	0.9 (0.8-1.0)	0.043
Bodily pain	Any symptom at baseline	2.2 (1.2-3.9)	0.010
	LVEF per 10%	1.3 (1.0-1.8)	0.032
Mental health	-	-	-
Social functioning	Any symptom at baseline	2.2 (1.2-4.0)	0.007
	Age per 10 year	0.6 (0.4-0.9)	0.007
Emotional role limitation	Any symptom at baseline	2.7 (1.5-4.6)	<0.001
Vitality	-	-	-
Worsening in SF-36			
General Health	Any symptom at end of study	2.5 (1.4-4.3)	0.002
	Diabetes mellitus	2.4 (1.0-5.0)	0.041
	Septum per mm	1.1 (1.0-1.3)	0.034
Physical functioning	Any symptom at end of study	2.0 (1.2-3.2)	0.007
	Age per 10 year	1.7 (1.2-2.5)	0.003
Physical role limitation	Any symptom at end of study	1.9 (1.1-3.1)	0.017
	Age per 10 year	1.6 (1.1-2.3)	0.016
Bodily pain	Any symptom at end of study	2.0 (1.2-3.3)	0.007
Mental health	Any symptom at end of study	2.1 (1.2-3.6)	0.011
	Female sex	2.3 (1.3-4.2)	0.004
	LVEF per 10%	0.7 (0.5-0.9)	0.004
	Major bleeding during study	5.0 (1.7-23.7)	0.041
Social functioning	Any symptom at end of study	2.0 (1.1-3.5)	0.023
	Previous hospitalization for HF	2.7 (1.1-6.2)	0.025
	Arrhythmic event during study*	4.4 (1.2-15.8)	0.024
	Beta-blocker use	2.6 (1.4-4.6)	0.002
Emotional role limitation	Any symptom at end of study	1.9 (1.1-3.3)	0.027
	Previous hospitalization for HF	2.6 (1.1-5.9)	0.024
Vitality	Any symptom at end of study	2.0 (1.2-3.2)	0.008

* arrhythmic event defined as syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation.
LVEF - Left ventricular ejection fraction, HF – Heart failure

Table 5. Patient characteristics associated with a relevant improvement or worsening in MFI-20 from baseline to end of study, described in odds ratio

	Determinants of change	OR (95% CI)	P Value
Improvement in MFI-20			
General fatigue	-	-	-
Physical fatigue	-	-	-
Reduced activity	-		
Reduced motivation	-	-	-
Mental fatigue	LVEF per 10%	0.8 (0.6-1.0)	0.033
Worsening in MFI-20			
General fatigue	Any symptom at end of study	2.5 (1.5-4.2)	<0.001
	Age per 10 year	1.4 (1.0-2.0)	0.045
Physical fatigue	Any symptom at end of study	2.2 (1.4-3.7)	0.002
	No symptoms at baseline	1.7 (1.0-2.8)	0.036
	Age per 10 year	1.6 (1.1-2.3)	0.008
	No CAD	3.1 (1.6-6.3)	0.001
Reduced activity	Diabetes mellitus	2.9 (1.3-6.4)	0.008
	Septum per mm	1.1 (1.0-1.2)	0.036
Reduced motivation	Age per 10 year	1.7 (1.2-2.4)	0.002
Mental fatigue	Female sex	1.6 (1.0-2.6)	0.039

CAD – Coronary artery disease; CI - confidence interval; LVEF - Left ventricular ejection fraction

Symptoms at baseline, absence of symptoms at end of study, higher left ventricular ejection fraction, lower age, and a thinner septum were determinants of improvement of the SF-36 (Table 4). Worsening of the subscales of the SF-36 were associated with the presence of symptoms at end of study, higher age, diabetes mellitus, thicker septum, female sex, lower left ventricular ejection fraction, beta-blocker use, hospitalization for heart failure, major bleeding and an arrhythmic event during the study (Tables 4).

Improvements in the AF severity scale were associated with symptoms at baseline (OR 4.1, 95% CI 2.2-7.4, p<0.001) and lower age (per 10 year OR 0.7, 95% CI 0.5-0.9, p= 0.019). Worsening in the AF severity scale were associated with symptoms at end of study (OR 3.1, 95% CI 1.8-5.3, p<0.001). Worsening of the subscales of the MFI-20 were associated with the presence of symptoms at end of study, higher age, diabetes mellitus, thicker septum, female sex and lower left ventricular ejection fraction (Tables 5). Improvements and worsening were not associated with heart rate at the end of dose-adjustment phase or randomization strategy in any of the questionnaires used. Also a relevant heart rate reduction was not associated with improvements or worsening of quality of life in any of the questionnaires used.

Discussion

The present analysis of the RACE II study suggests that stringency of rate control does not affect quality of life during treatment of patients with permanent AF. Of note, heart rate was not related to formal quality of life measures, both at inclusion and follow-up. In contrast, straightforward clinical AF symptoms did relate to formal quality of life measures, both at inclusion as well as during follow-up. However, symptoms were not affected by stringency of rate control and therefore, type of rate control did not affect quality of life. During follow-up minor changes in quality of life occurred, but again, stringency of rate control was not influential. In stead, changes in quality of life were related to age, symptoms at baseline and at end of study, severity of underlying disease and female sex.

Quality of life in permanent atrial fibrillation

Compared to healthy subjects quality of life is reduced in patients with AF.[2,3] Previous studies in patients with AF have shown that quality of life is comparable between rhythm and rate control strategies,[3,4] although sinus rhythm is associated with an improvement in quality of life.[3,5,6] There are, however, no prospective studies on the effect of stringency of rate control on quality of life. In a post-hoc analysis of AFFIRM no significant relation between heart rate and quality of life was found.[20] A comparable subanalysis in the rate control arm of the first RACE study also showed no relation between achieved heart rate and quality of life.[21] We also did not observe, in any of the questionnaires used in the present analysis, a relation between heart rate and quality of life, or rate control strategy and quality of life, not at baseline, nor at study end. In contrast, age, symptoms at baseline and at end of study, severity of underlying disease and female sex influenced quality of life.

Why does heart rate and stringency of heart rate control not affect quality of life in AF? One explanation from our data is that permanent AF patients may lack typical AF symptoms.[22] In our study cohort almost half of the patients did not have AF related symptoms and overall patients were not highly symptomatic (see below). The lack of significant symptoms obviously limits the impact of rate control with respect to improving quality of life, irrespective of strategy. In addition, symptoms may be driven by underlying heart disease rather than the arrhythmia itself. This is reflected in the fact that dyspnea and fatigue were far more frequent than typical AF related palpitations. Finally, controlling rate does not preclude patients from being symptomatic due to ventricular irregularity and the latter may not be affected by stringency of rate control. In contrast to the above, however, our data do not rule out that strict rate control may have a beneficial effect on AF symptoms and quality of life in highly symptomatic AF patients, and that, on the other hand, more and higher dosages of rate control drugs may have negatively affected quality of life in the strict group. This is illustrated by the

association between worsening of social functioning and beta-blocker use, which may be caused by more symptoms of fatigue and a reduction in exercise capacity caused by beta-blockers.[19]

Patients included in RACE II were not highly symptomatic. About 40% of the included patients did not experience symptoms due to AF at all. This is also reflected in the scores of the SF-36 and the MFI-20 questionnaire. However, scores of both the SF-36 and the MFI-20 were less favourable compared to the general population,[13,23] but comparable to the scores found in patients with cancer.[24] Patients with chronic fatigue and patients with moderate heart failure, however, had less favourable scores on the MFI-20 questionnaire as compared to our patients.[16,25] The relatively low symptom burden is also reflected in the scores on the AF severity scale in our study. A previous study in patients with highly symptomatic paroxysmal AF reported scores as high as 12 on the AF severity scale.[17] Patients with permanent AF are well known to have less often symptoms as compared to paroxysmal AF.[22,26] Furthermore, the type of symptoms is different between patients with paroxysmal and permanent AF. Palpitations are the main complaint in paroxysmal AF, as compared to dyspnea in patients with persistent or permanent AF,[26] which was also the case in our patient group. Notwithstanding the above, presence of symptoms was related to quality of life as well as changes in quality of life over time and the latter was not affected by stringency of rate control. Obviously, in highly symptomatic patients with uncontrolled heart rate well above 110 at rest, rate control would significantly affect quality of life. However, our study did not focus on these highly symptomatic acute patients in whom some sort of rate control is unavoidable. In stead, we included patients with on average 2-3 months of AF with or without rate control drugs who - as a matter of daily clinical fact - were relatively stable. The present analysis suggests that type of rate control does not matter in terms of improvement in quality of life.

Gender importantly influenced quality of life. In the general population women also showed a lower quality of life.[27] In addition, previous AF trials showed lower quality of life in women compared to men with persistent AF, [3,28,29] and with paroxysmal AF.[28] In the Euro Heart Survey on Atrial Fibrillation,[30] and in a Canadian cohort women also demonstrated to have a lower quality of life.[31] It is still unknown why women with AF have a lower quality of life. Comparable observations are known from women with a previous myocardial infarction.[32] Since men are often overrepresented in clinical trials, more data on women are clearly warranted.

Limitations

The outcome of this quality of life analysis can not be generalized to all patients with AF, since all patients had permanent AF and were not highly symptomatic. A trial evaluating high and low heart rates in AF would ideally bring all patients to the relevant heart rate targets. Although the differences in achieved heart rates between both groups were smaller than might have been expected, strategies to achieve the

heart rate targets were completely different, which may have led to differences in quality of life between both groups. Although the quality of life questionnaires we used are validated, it remains possible that these questionnaires were too insensitive to detect true changes in quality of life.

Conclusion

In patients with permanent AF quality of life are not affected by stringency of rate control. In stead, symptoms, female sex, age, severity of underlying disease, and occurrence of endpoints were associated with worsening of quality of life.

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Does Better Rate Control Improve Quality of Life?

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5B

"Cure sometimes, treat often, comfort always." Hippocrates[1]

Guidelines for the management of atrial fibrillation (AF) increasingly emphasize patient well-being as one of the most important outcomes of successful therapy. Unfortunately, no AF therapy has been clearly shown to reduce mortality, and data demonstrating a reduction in major morbidity, apart from the clearly understood reduction of stroke, are limited.[2,3] Practitioners are thus aware that a primary goal of AF management is to reduce or mitigate symptoms related to AF and its treatment. For most patients, this will involve slowing of the rapid and irregular ventricular rate that usually accompanies AF, either as the initial or the exclusive goal of treatment (in addition to the crucially important need to assess stroke risk and treat appropriately). However, patient well-being, often expressed as health related quality of life (QOL), is difficult to measure precisely or even describe using commonly understood terminology. Components of QOL are by definition subjective, and understanding the impact of the AF condition in a particular patient requires the disentanglement of those aspects of the illness that are directly or indirectly related to AF from other symptoms or difficulties related to coexisting llnesses (e.g., heart failure, pulmonary disease), symptoms or mental states associated with other health-related problems, or the effect of issues such as physical deconditioning, emotional difficulties, and financial problems on health status. Furthermore, an accurate understanding of the impact of AF requires that patients be able and willing to accurately articulate the extent to which the illness affects their daily life functioning, as well as their assessment of the consequences the illness and its treatment have on their individual perceived health status. This is a difficult task.

It is tempting, and seems at first glance reasonable, to use readily available and objective measures of cardiac function in patients with AF as a surrogate for the assumed impact on QOL. For example, many physicians may assume that a rapid and irregular heart rate is undesirable, and implicitly subjectively undesirable, compared with a slower, more well-controlled rate. Similarly, it is often assumed that sinus rhythm maintenance and restoration ought to be associated with better QOL than persisting AF. Groenveld et al.,[4] in the current issue of the Journal, have contributed importantly to our understanding of the connection between objective, electrocardiography-based measures of cardiac function and subjective patient-related outcomes. In a substudy of the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study (a randomized trial of "strict" versus "lenient" rate control in patients with permanent AF), they have added to the primary observation that "strict rate control" (targeting a resting heart rate of <80 beats/min) compared with "lenient rate control" (targeting a heart rate of <110 beats/min at rest) does not produce meaningful improvement in major morbidity and mortality.[5] In this companion study, they assessed QOL in 437 of the 614 patients enrolled in the RACE II study, using

both generic measures of QOL, such as the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), and more disease-related measures, including the AF severity scale and the Multidimensional Fatigue Inventory-20, at baseline and during long-term follow-up. In short, there were no differences in general or disease-specific measures of QOL or symptoms between the strict and lenient rate control groups, and no meaningful changes over time in these measures. QOL, as well as changes in this factor, was, however, related to age, the severity of underlying heart disease, the severity of symptoms, and sex. These results are consistent with observations that have been made in both cross-sectional and longitudinal studies of patients with AF (population-based cohort studies as well as randomized studies), which have shown that the strategy of AF treatment (i.e., rate vs. rhythm control strategy) has limited to no impact on QOL, and that the most important determinant of general QOL is the degree of symptoms specifically related to AF (e.g., dyspnea, palpitations, fatigue).[6,7] In the FRACTAL (Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle) cohort study of 963 patients with AF, the presence of AF and the "AF burden" was not related to impairment in QOL,[8] similar to observations from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study.[7] There are some limitations to our ability to generalize from the important observations of Groenveld et al.[4] First, patients in this study had long-standing permanent AF, a condition that has been suggested to be less consequential on QOL than paroxysmal or persistent AF early in the disease onset. Second, the differences in average ventricular rate between the "strict" and the "lenient" groups of patients were relatively modest, potentially limiting the ability to perceive potential differences in QOL that may be present between heart rates in the normal range (e.g., 60 to 70 beats/min) and heart rates near the upper limit of guideline-recommended rates for adequate rate control (e.g., 100 to 109 beats/min). Patients in the RACE II trial had impaired QOL, but overall SF-36 scores were intermediate between age-standardized normal controls and SF-36 scores in patients reported in previous trials of AF, including in the RACE I study of rate versus rhythm control published by the same research group.[9] The results of this trial may thus apply primarily to patients with long-standing and not terribly symptomatic AF.

However, in support of the generalizability of the results from Groenveld et al.,[4] previous studies of the relation between heart rate and outcomes have shown directionally similar results. For example, there is no relation between heart rate and exercise capacity as measured by maximum oxygen consumption in patients with AF.[10] Other studies have also failed to note a relation between heart rates at rest and with exercise,[11] or the ventricular rate after treatment,[12] and general well-being. In a large cohort study of patients with recent-onset AF, baseline heart rate was not related to QOL.[13] In a study of various therapies to slow ventricular responses during exercise, beta-blockers were more effective than calcium-channel blockers at limiting maximum exercise heart rate but were not associated with changes in QOL or exercise tolerance, whereas calcium-channel blockers tended to improve QOL.[11] In a summary analysis of multiple small randomized trials of digoxin, beta-blockers, and calcium-channel blockers for rate control during exercise in AF, beta-blockers were

more effective at slowing peak ventricular response but did not increase or decrease maximum exercise tolerance. Calcium-channel blockers, conversely, were less effective at heart rate slowing but improved or had no effect on exercise tolerance.[14] These observations suggest that, at least for betablocker therapy, the potential benefits of stricter rate control on exercise capacity and well-being may be offset by adverse effects such as fatigue or effort intolerance. The lack of QOL benefit from strict rate control in the RACE II study may in part be due to a potential symptomatic benefit from lower heat rates offset by adverse effects resulting from the need for more frequent use of beta-blockers, in higher doses, in the strict rate control group compared with the lenient rate control group.

In contrast to the disconnect between rate and rhythm and QOL, studies consistently show that there are individual patient characteristics that tend to be associated with poor QOL in AF. The most prominent of these are female sex, invariably associated with poorer QOL than in men for the same apparent degree of illness burden,[8,15,16] the presence of depression or pessimism as a stable personality trait,[17] and personality traits relating to the response to physical and emotional stressors, such as anxiety sensitivity and somatization,[18] as well as more obvious factors, such as the presence of heart failure and coexisting illnesses, which are associated with poorer QOL. Older patients are often less symptomatic than younger patients and tend to have a different symptom pattern, with fatigue and dyspnea being more prominent, whereas palpitations (an unpleasant awareness of cardiac action) is more prominent in younger patients.[8,16]

Treatment of AF by catheter ablation may prove to be an exception to the disappointingly small effect of strict rate or rhythm control on QOL. Among patients with symptomatic, medically refractory paroxysmal AF, catheter ablation has been associated with a marked and sustained improvement of QOL.[19] However, these results are tempered by a recent study of 323 patients in which the improvement of SF-36 QOL indices was unrelated to the ablation outcome itself.[20] This finding highlights the difficulty in objectively assessing the QOL effect of AF ablation and raises the possibility that the QOL benefits of AF ablation may in part be related to a placebo effect of the procedure.[20]

What clinical lessons can we draw from the observations of Groenveld et al.?[4] Most important, it is insufficient to merely examine the electrocardiogram of patients in AF to assess the impact of their illness on their well-being. For example, a resting ventricular response rate in AF of 100 beats/min does not necessarily imply the patient is worse off than if his or her heart rate was 60 beats/min and should not necessarily prompt the practitioner to intensify rate control therapy. Because QOL is subjective, it has to be assessed subjectively. There is no laboratory test, per se, for QOL. Questionnaires used in research studies are valid measures of the seemingly ethereal concept but are impractical for routine clinical use. Global bedside estimations of QOL have been proposed, including the Canadian Cardiovascular Society's Severity of Atrial Fibrillation scale[21] and the European Society of Cardiology's European Heart Rhythm Association scale.[2] These are simple-to-use global measures of the impact of AF and its treatment on patient well-being. Clinicians need to be aware that patient

personality, treatment expectations, and factors unrelated to the arrhythmia itself will have important, potentially determining influences on the extent to which AF causes suffering.

In an era of increasingly sophisticated and complex technologies used to investigate and treat atrial fibrillation, it is worth heeding the advice of Hippocrates[22]: "It is far more important to know what person the disease has than what disease the person has."

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6 All-cause Mortality and Hospitalizations in Patients with Permanent Atrial Fibrillation Data of the RACE II study

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Abstract

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and associated with an increased morbidity and mortality. We investigated differences in all-cause mortality and cardiovascular hospitalization between patients with permanent AF treated with lenient versus strict rate control.

Methods

In the current analysis the primary outcome was a composite of all-cause mortality and cardiovascular hospitalization. The outcome events include the first event for each patient. Cardiovascular hospitalizations were determined by primary diagnosis at discharge. All 614 patients were included in the present analysis, 311 patients were randomized to lenient rate control (resting heart rate <110 beats per minute [bpm]), and 303 to strict rate control (resting heart rate <80 bpm and during moderate exercise <110 bpm).

Results

Mean age was 68±8 years, 66% were male and 61% had hypertension. During a median follow-up of 2.9 years all-cause mortality and cardiovascular hospitalization occurred in 64 of 311 (21.7%) in the lenient group and 67 of 303 (23.5%) patients the strict group (p=0.6). All-cause mortality occurred in 17 (5.6%) versus 18 (6.6%) in the lenient versus strict group, cardiovascular hospitalization in 57 (21.0%) versus 57 (22.2%), respectively. There was also no difference in the total number of all-cause hospitalization 96 (33.4%) versus 105 (38.2%) in the lenient versus strict group.

Conclusion

There is no difference in all-cause mortality and cardiovascular hospitalization between lenient and strict rate control, again in favor of lenient rate control being frontline therapy in patients with permanent AF. Hospitalizations are common in this frail patient group.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, and its prevalence is increasing.[1] AF is not benign and is associated with a doubled risk of death and an increased risk of cardiovascular hospitalizations especially due to stroke, heart failure and bleeding.[1-4] The latter is caused by the associated co-morbidities as well as the arrhythmia itself.[5-10] This leads to frequent hospitalizations, in turn being a burden on the health care system.[11,12] The aim of the current post-hoc analysis was to explore the incidence of all-cause mortality and cardiovascular hospitalizations in patients with permanent AF included in the RACE II and to assess differences between lenient and strict rate control.

Methods

RACE II study design

The study design and results of the RACE II have been published previously.[13,14] The study was approved by the institutional review boards of all participating centers, and all patients gave written informed consent. Eligibility criteria were permanent AF for up to 12 months, age of 80 years or younger, mean resting heart rate >80 beats per minute, and current use of oral anticoagulation therapy. The rate control targets in the strict group were a resting heart rate <80 beats per minute, and a heart rate <110 beats per minute during moderate exercise. The rate control target in the lenient group was a resting heart rate <110 beats per minute. During the dose-adjustment phase, patients were administered one ore more negative dromotropic drugs (i.e., beta-blockers, nondihydropiridine calcium-channel blockers, and digoxin), used alone or in combination and at various doses, until the heart rate targets were achieved. Follow-up at the outpatient department occurred every 2 weeks until the heart rate targets were achieved. After the dose-adjustment phase follow-up outpatient visits occurred after 1, 2, and 3 years. Follow-up was terminated after a follow-up period of 3 years or on June 30, 2009, whichever came first.[13,14]

The primary outcome in RACE II was a composite of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation. All reported primary outcome events were adjudicated by an independent adjudication committee unaware of the randomized treatment assignments.

A total of 614 patients were included in the RACE II, 303 were randomized to strict rate control and 311 to lenient rate control. The primary outcome was reached in 81 patients (43 in the strict and 38 patients in the lenient rate control group). The cumulative incidence of the primary outcome at 3 years was 14.9% in the strict and 12.9% in the lenient rate control group. This confirmed the hypothesis of non-inferiority of lenient rate control as compared to strict rate control.[14]

Table 1. Baseline characteristics

	Lenient rate control (n=311)	Strict rate control (n=303)	P Value
Age – yr	69±8	67±9	0.1
Male sex – no. (%)	205 (65.9)	198 (65.3)	0.9
Total atrial fibrillation duration (months)	16 (6 – 54)	20 (6 – 64)	0.2
Duration permanent atrial fibrillation (months)	3 (1-6)	2 (1-5)	0.2
Previous electrical cardioversions ≥1 – no. (%)	221 (71.1)	220 (72.6)	0.6
Hypertension – no. (%)	200 (64.3)	175 (57.8)	0.1
Coronary artery disease – no. (%)	67 (21.5)	44 (14.5)	0.024
Valvular heart disease – no. (%)	64 (20.6)	60 (19.8)	0.8
Chronic obstructive pulmonary disease – no. (%)	36 (11.6)	43 (14.2)	0.3
Diabetes mellitus – no. (%)	36 (11.6)	32 (10.6)	0.7
Lone atrial fibrillation* – no. (%)	5 (1.6)	6 (2.0)	0.7
Previous heart failure hospitalization – no. (%)	28 (9.0)	32 (10.6)	0.6
$CHADS_2$ score† – no. (%)	1.4±1.0	1.4±1.2	0.6
0 or 1	178 (57.2)	195 (64.4)	0.3
2	94 (30.2)	65 (21.6)	
3-6	39 (12.5)	43 (14.2)	
Symptoms – no. (%)	173 (55.6)	175 (57.8)	0.8
Palpitations	62 (19.9)	83 (27.4)	0.03
Dyspnea	105 (33.8)	109 (36.0)	0.5
Fatigue	86 (27.7)	97 (32.0)	0.2
Body mass index – kg/m^2	29±5	29±5	0.8
Blood pressure – mmHg			
Systolic	137±19	135±16	0.2
Diastolic	85±11	82±11	0.003
Heart rate in rest – beats per minute	96±14	96±12	0.5
New York Heart Association functional class			
I – no. (%)	206 (66.2)	194 (64.0)	0.6
II – no. (%)	89 (28.7)	96 (31.7)	
III – no. (%)	16 (5.1)	13 (4.3)	

* Lone atrial fibrillation was defined as AF in the absence of cardiovascular disease and extracardiac precipitating causes of AF.
† The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing al the points for a given

Table 1. Baseline characteristics (continued)

	Lenient rate control (n=311)	Strict rate control (n=303)	P Value
Rate control medications in use – no. (%)			
No rate control drugs	36 (11.6)	27 (8.9)	0.3
Beta-blocker alone	140 (45.0)	136 (44.9)	0.9
Verapamil/diltiazem alone	18 (5.8)	19 (6.3)	0.8
Digoxin alone	20 (6.4)	24 (7.9)	0.5
Beta-blocker + verapamil/diltiazem	7 (2.3)	11 (3.6)	0.3
Beta-blocker + digoxin	53 (17.0)	49 (16.2)	0.7
Verapamil/diltiazem + digoxin	14 (4.5)	14 (4.6)	0.9
Beta-blocker + verapamil/diltiazem + digoxin	2 (0.6)	5 (1.7)	0.2
Sotalol	18 (5.8)	13 (4.3)	0.4
Amiodarone	3 (1.0)	5 (1.7)	0.5
Other medications in use at baseline – no. (%)			
ARB or ACE inhibitor	166 (53.4)	140 (46.2)	0.1
Diuretic	134 (43.1)	113 (37.3)	0.1
Statin‡	103 (33.1)	74 (24.4)	0.017
Vitamin K antagonist	308 (99.0)	298 (98.3)	0.5
Aspirin	4 (1.3)	6 (2.0)	0.5
Echocardiographic parameters – mm			
Left atrial size, long axis	46±6	46±7	0.5
Left ventricular end-diastolic diameter	51±7	51±8	0.7
Left ventricular end-systolic diameter	36±8	36±9	0.9
Left ventricular ejection fraction – %	52±11	52±12	0.4
≤ 40% – no. (%)	45 (14.5)	48 (15.8)	0.5

ACE denotes angiotensin-converting enzyme inhibitor and ARB angiontensin-receptor blocker
‡ Statins are defined here as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors

Design of the current analysis

For the current analysis the primary outcome was a composite of all-cause mortality and cardiovascular hospitalizations. All hospitalizations and possible endpoints were (prospectively) reported to the Trial Coordination Center (University medical Center Groningen, the Netherlands) during the study and were adjudicated by an independent adjudication committee. Cardiovascular hospitalization was determined by study personnel by considering the primary diagnosis when reviewing the medical records of all hospitalizations during the study. Secondary outcome were all-cause

Table 2. Composite of all-cause mortality and cardiovascular hospitalization*

	Lenient rate control (n=311)	Strict rate control (n=303)	Hazard ratio
	No. of patients (%)		(95% CI)
Composite outcome	64 (21.7)	67 (23.5)	0.91 (0.65-1.28)
All-cause mortality	17 (5.6)	18 (6.6)	0.91 (0.47-1.77)
Death from cardiovascular cause	9 (2.9)	11 (3.9)	0.79 (0.33-1.91)
Cardiac arrhythmic death	3 (1.0)	4 (1.4)	
Cardiac nonarrhythmic death	1 (0.3)	2 (0.8)	
Noncardiac vascular death	5 (1.7)	5 (1.9)	
Non cardiac, non vascular death	8 (2.7)	7 (2.8)	1.11 (0.40-3.06)
Cancer	3 (1.0)	4 (1.4)	
Fatal infection	4 (1.3)	3 (1.0)	
Other	1 (0.3)	0	
Cardiovascular hospitalization	57 (21.0)	57 (22.2)	0.95 (0.66-1.37)
Heart failure	11 (3.8)	11 (4.1)	0.97 (0.42-2.24)
Cardiac surgery	5 (1.6)	2 (0.7)	
Stroke, TIA or systemic embolism	5 (1.9)	13 (4.7)	0.37 (0.13-1.04)
Severe bleeding	15 (5.3)	13 (4.5)	1.12 (0.53-2.34)
Minor bleeding requiring hospitalization	2 (0.7)	3 (1.0)	
Arrhythmic event†	16 (5.6)	16 (5.8)	0.96 (0.48-1.92)
ACS or elective PCI	5 (1.6)	2 (0.7)	
Atypical symptoms‡	6 (1.9)	6 (2.0)	
AF related hospitalization#	5 (1.6)	1 (0.3)	

ACS - acute coronary syndorme; CI - confidecnce interval; PCI - percutaneous coronary intervention; TIA - transient ischemic attack

* The composite primary outcome include the first event for each patient. In contrast, the tabulation of component events include all such events. The cumulative incidences were determined with the use of Kaplan-Meier analysis.

† Syncope, life threatening adverse effects rate control drugs, sustained ventricular tachycardia or ventricular fibrillation, pacemaker implantation, implantable cardioverter defibrillation implantation (primary or secondary prevention), non life threatening adverse event of rate control drugs drugs, reveal implantation

‡ Hospitalization for chest pain without ACS, hospitalization for collapse without trauma

\# Electrical cardioversion, pulmonary vein isolation, change in rate control drugs

hospitalizations and major and minor bleedings requiring hospitalization. A hospital admissions required ≥1 overnight stay to be accounted for a hospitalization. The outcome events included the first event for each patient. All patients included in RACE II were included in the present study.

Statistical analysis

Baseline descriptive statistics are presented as mean ± standard deviation (SD) or median (range) for continuous variables and counts with percentages for categorical variables. Differences between groups, in terms of patient characteristics, were evaluated by Chi-square test or McNemar's test, depending on normality and type of the data. Kaplan-Meier analysis was performed to assess differences in outcome between the randomization strategies. In all analyses a value of $p<0.05$ was considered statistically significant.

Results

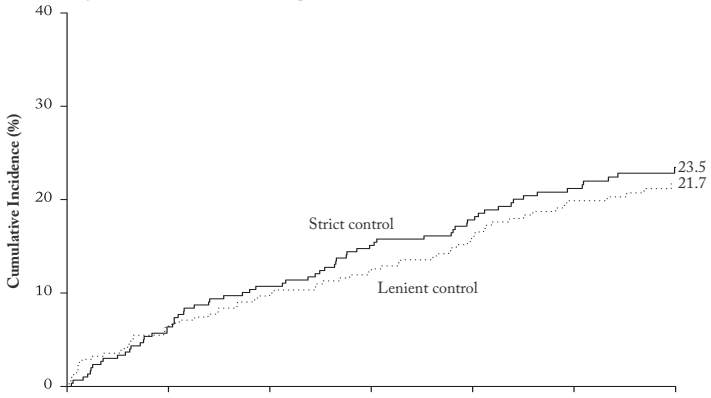
Patient characteristics

In total 614 patients were included in the current study, 311 patients were randomized to lenient rate control and 303 to strict rate control (Table 1). Median follow up was 3.0 (interquartile range 2.4-3.0) years. Clinical characteristics were almost comparable between the groups, with the exception of coronary artery disease, statin use and a slightly higher diastolic blood pressure in the lenient group.

Primary outcome

The primary outcome of all-cause mortality and cardiovascular hospitalization was reached in a total of 131 patients (64 of 311 in the lenient and 67 of 303 in the strict group) in the present study (Table 2). In Figure 1 the Kaplan-Meier curves for the primary outcome are shown, according to lenient and strict rate control. The cumulative incidence of the primary outcome was 21.7% in the lenient and 23.5% in the strict group (p=0.6).

Figure 1. Primary outcome according to lenient and strict rate control



No. at Risk							
Strict control	303	279	266	251	236	199	117
Lenient control	311	290	279	272	245	207	126

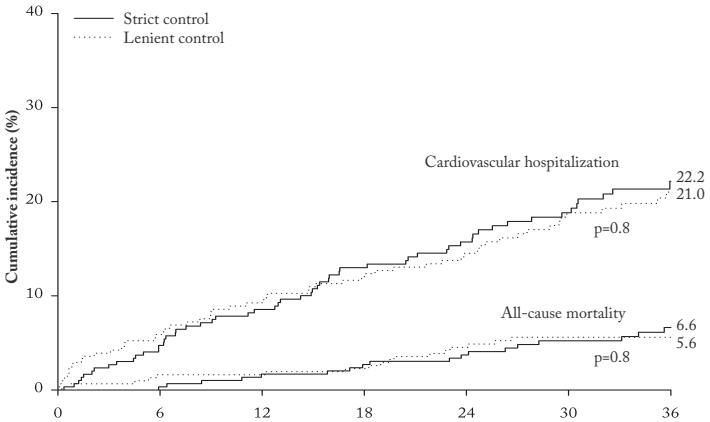
In the lenient group 17 patients (5.6%) died during follow-up, as compared to 18 (6.6%) in the strict group (p=0.8). Cardiovascular hospitalization occurred in 57 (21.0%) patients in the lenient group, and in 57 (22.2%) patients in the strict group (Figure 2, p=0.8). Cardiovascular hospitalizations were predominantly caused by hospitalizations for heart failure, stroke, bleeding and arrhythmic events. AF related hospitalizations occurred seldom. There were no differences between both randomization groups. Non-cardiovascular death was mostly due to a malignancy or infection (Table 2).

All cause hospitalization and bleeding

A total of 201 patients were hospitalized during the study. First hospitalization occurred in 96 (33.4%) in the lenient, and 105 (38.2%) in the strict group (p=0.3). In the lenient group 60 (22.7%) patients were hospitalized for non-cardiovascular reasons, and 66 (26.6%) patients in the strict group (Figure 3, p=0.4).

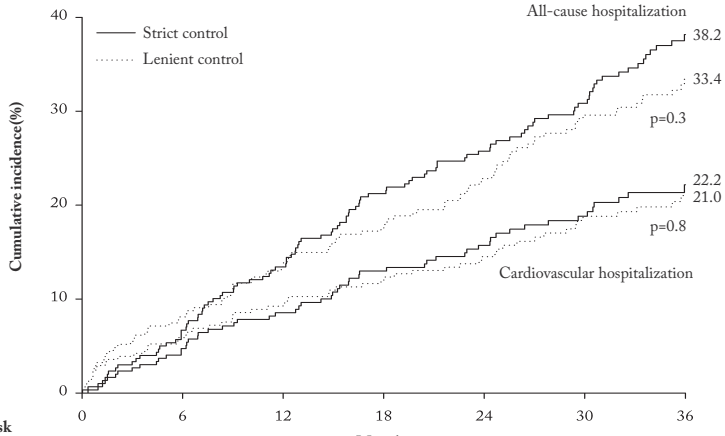
In total 32 bleedings occurred during the study, 28 major and 5 minor bleedings were reported. There was no difference between the 2 randomization strategies in the occurrence of bleedings (Table 3). There was also no difference in life threatening or gastrointestinal bleedings between the randomization strategies (Table 4).

Figure 2. All-cause mortality and cardiovascular hospitalization according to lenient and strict rate control



No. at Risk							
Cardiovascular hospitalization							
Strict control	303	279	266	251	236	199	117
Lenient control	311	290	279	272	245	207	126
All-cause mortality							
Strict control	303	297	294	287	275	240	146
Lenient control	311	305	304	303	278	245	175

Figure 3. All-cause hospitalization and cardiovascular hospitalization according to lenient and strict rate control



No. at Risk							
All-cause hospitalization							
Strict control	303	278	256	228	207	168	89
Lenient control	311	282	265	253	221	180	104
Cardiovascular hospitalization							
Strict control	303	279	266	251	236	199	117
Lenient control	311	290	279	272	245	207	126

Table 3. All hospitalizations during study

	Lenient Rate Control (n=311)	**Strict Rate Control (n=303)**	**Hazard ratio**
	No. of patients (%)		(95% CI)
All Hospitalizations*	96 (33.4)	105 (38.2)	0.86 (0.65-1.14)
Cardiovascular#	57 (21.0)	57 (22.2)	0.95 (0.66-1.37)
Non-cardiovascular#	60 (22.7)	66 (26.6)	0.86 (0.60-1.21)
Surgery	39 (14.4)	40 (17.4)	
Orthopedic	9 (2.9)	11 (3.6)	
Cancer	7 (2.3)	9 (3.0)	
Other surgery	23 (7.4)	20 (6.6)	
Infection	22 (7.1)	24 (7.9)	
Pneumonia	13 (4.2)	12 (4.0)	
Other infection	9 (2.9)	12 (4.0)	
Other	4 (1.6)	4 (1.5)	

* First event for each patient
# All hospitalizations during study with ≥1 overnight stay
CI - confidence interval

Table 4. Bleedings during study

	Lenient Rate Control (n=311)	Strict Rate Control (n=303)	Hazard ratio
	No. of patients (%)		(95% CI)
Major bleeding	15 (5.3)	13 (4.5)	1.12 (0.53-2.34)
Life threatening	1 (0.3)	4 (1.5)	
Non-life threatening	14 (5.0)	9 (3.1)	
Gastrointestinal*	4 (1.6)	4 (1.5)	
Post surgery	5 (1.6)	1 (0.3)	
Minor bleeding	2 (0.7)	3 (1.0)	
Major or minor bleeding	16 (5.6)	16 (5.6)	0.96 (0.48-1.93)
Intracranial	0	3 (1.0)	
Extracranial	15 (5.3)	10 (3.5)	

* gastrointestinal bleedings could be life threatening and non-life threatening

Discussion

The present analysis of RACE II showed no difference in all-cause mortality and cardiovascular hospitalization between lenient and strict rate control in patients with permanent AF. In addition, no differences in all-cause hospitalizations were observed. Of note, hospitalizations occurred frequently in this group of AF patients.

We observed 22% cardiovascular hospitalizations during the study. In the Euro Heart survey cardiovascular hospitalization was higher (35%). However, AF related hospitalizations (17%) were very frequent, also in the patients with permanent AF.[6] A post hoc analysis of AFFIRM also showed a higher incidence of cardiovascular hospitalization, however, when excluding hospitalizations related to treatment strategy (rhythm or rate control) the hospitalization rate dropped. In addition, follow-up was longer in AFFIRM as compared to the present study.[15] Hospitalization rate in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) was around 60% as compared to 22% in the current study. This large difference may be explained by the relative low number of patients with heart failure in our cohort. In addition, 30% of patients had paroxysmal AF in the AF-CHF, as compared to 100% permanent AF in the present study. Patients with paroxysmal AF are more often hospitalized as compared to patients with permanent AF.[6] In addition, in the present cohort of patients with permanent AF, cardiovascular hospitalization was mainly for heart failure, stroke and bleeding. Patients with paroxysmal or persistent AF are more frequently hospitalized for AF interventions.[6]

AF related hospitalizations were not common in our patient group. Considering this, the arrhythmia was recently accepted, i.e. had become permanent. This may imply that acceptance of AF creates a more stable situation with less AF related hospitalization. A post-hoc analysis of the AF-CHF and Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) showed that patients treated with a rate control strategy were less often hospitalized as compared to patients treated with a rhythm control strategy.[15,16] The same was observed in the AF-CHF study.[16] This may also explain the relative low cardiovascular hospitalization rate in our cohort.

Why was there no difference in all-cause mortality and cardiovascular hospitalization between lenient and strict rate control? First, mortality in patients with AF is determined by underlying disease rather than heart rate.[7,17-19] Post-hoc analyses of both AFFIRM and the Rate Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) showed no difference in outcome between patients with a higher or lower heart rate.[17,18] A pooled analysis of these trials confirmed these findings.[19]

Second, the cardiovascular hospitalizations in RACE II are largely determined by bleedings, strokes and heart failure.[14] Development of heart failure was one of the main concerns of lenient rate control. Our results show that a heart rate below 110 beats per minute was low enough to prevent overt heart failure. This is in line with previous studies on heart failure and beta-blocker, which show no survival benefit of beta-blockers in patients with AF.[20-22] Due to the loss of atrial kick and ventricular frequency, patients with AF and heart failure may require a higher heart rate.[23]

It should be noted that in the present patient cohort one in every three patients is hospitalized for a serious cardiovascular or non-cardiovascular event. This indicates that co-morbidities are prevalent in patients with permanent AF. In addition, most hospitalizations for non-cardiovascular reasons were for surgery or infection. Due to the prevalent use of oral anticoagulation this is a critical moment in patients with AF. Temporarily cessation of oral anticoagulation or drug interactions, risk of bleeding and stroke may be elevated. Furthermore, the majority of non-cardiovascular death is attributable to cancer and infections. Regarding the above, this should remind us that AF patients are a high risk group.

How does the current study add to the main results of RACE II? The non-inferiority of lenient rate control to strict rate control was groundbreaking.[14,24] However, a composite primary outcome was used. The current study shows no difference in all-cause mortality, the most firm outcome parameter. In addition, there was no difference in cardiovascular hospitalization. Previous studies have shown that cardiovascular hospitalization is a useful surrogate outcome for mortality in patients with AF.[15,25,26] Therefore, the present data strengthen the rationale for a lenient rate control in patients with permanent AF.

Limitations

The RACE II was not designed to assess differences in all-cause mortality and cardiovascular hospitalizations between lenient and strict rate control. In addition, there was no pre-defined definition of cardiovascular hospitalization.[15,25,26]

Conclusion

Patients with permanent AF are frequently hospitalized for cardiovascular and non-cardiovascular events. There is no difference in the occurrence of cardiovascular hospitalization and mortality between patients with permanent AF randomized to lenient or strict rate control. Since strict rate control does not improve prognosis, lenient rate control should be used as frontline rate control strategy.

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Discussion

The aim of this thesis was to evaluate the effect of lenient and strict rate control on cardiovascular morbidity, mortality and quality of life in patients with permanent atrial fibrillation (AF). The rate versus rhythm control trials established the non-inferiority of rate control compared to rhythm control. Therefore, rate control is adopted as a frontline therapy in older patients without severe AF associated symptoms. However, the optimal level of heart rate control was unknown. The guidelines advised a more strict rate control approach, but this was not evidence based.[1] The strict rate control approach was recommended to reduce symptoms, improve quality of life and exercise tolerance, reduce heart failure, and improve survival.[1] On the other hand, strict rate control may induce more drug-related adverse effects, including bradycardia, syncope, and a need for pacemaker implantation. Therefore, the benefit and risk balance in terms of cardiovascular morbidity and mortality remained unclear.

In order to investigate the optimal heart rate during permanent AF, first, we performed a retrospective analysis of patients with permanent AF. The study cohort comprised all patients in the RACE trial randomized to rate control. The heart rate criterion in RACE for adequate rate control was a resting heart rate <100 beats per minute. There was no difference in outcome between patients with a mean resting heart rate <80 beats per minute versus ≥80 beats per minute (**chapter 2**). We then showed, in The Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient versus Strict Rate Control II (RACE II), a prospective, randomized, open label, clinical trial, the non-inferiority of lenient compared to strict rate control regarding cardiovascular morbidity and mortality (**chapter 3**). The difficulty to achieve strict rate control could have influenced the outcome of the RACE II, in favor of lenient rate control. Previous trials investigating strict rate control showed that about two-thirds of patients achieve the strict rate control criteria.[2] Adequate rate control was achieved in 67% of patients randomized to strict rate control in RACE II. Notably, there was no difference in outcome between patients with successful strict, failed strict, and lenient rate control. Also of importance, there was no difference in quality of life between the groups (**chapter 4**). Considering the equality in the primary outcome of the RACE II, patient welfare is important when instituting rate control. Therefore, the absence of differences in quality of life between lenient and strict rate control is of major importance (**chapter 5**). In an additional post-hoc analysis of the RACE II study we observed no differences in all-cause mortality and cardiovascular hospitalizations between lenient and strict rate control (**chapter 6**).

Rate Control in Atrial Fibrillation

The first report on AF has been written more than 100 years ago. Already at that time AF was a common condition in hospitalized patients.[3] In the beginning of the 20th century, treatment of AF consisted of rhythm control with quinidine and control of the ventricular rate with digoxin.[4,5] It was not until the 1960's that the electrical cardioversion was introduced.[6] However, electrical cardioversion was not always

successful.[7,8] Furthermore, conversion to sinus rhythm was often not permanent.[6] Only 30% of patients remained in sinus rhythm, regardless of serial cardioversions and antiarrhythmic drugs.[9]

During AF several hemodynamic changes occur which lead to symptoms of the patient. The atrial contribution to the total stroke volume is about 20-40%. This is absent during AF. Furthermore, the irregular ventricular rhythm during AF reduces the cardiac output, irrespective of heart rate.[10] These two factors may lead to a significant reduction in cardiac output. The reduction in cardiac output may be even more evident in patients with a reduced left ventricular ejection fraction or impaired diastolic function.[1] Since one of the key risk factors for AF is hypertension,[11,12] and hypertensive patients often have an impaired diastolic function,[13] this is of importance in patients with AF. Thus to maintain a comparable cardiac output, the heart rate may have to be higher during AF than during sinus rhythm.[14]

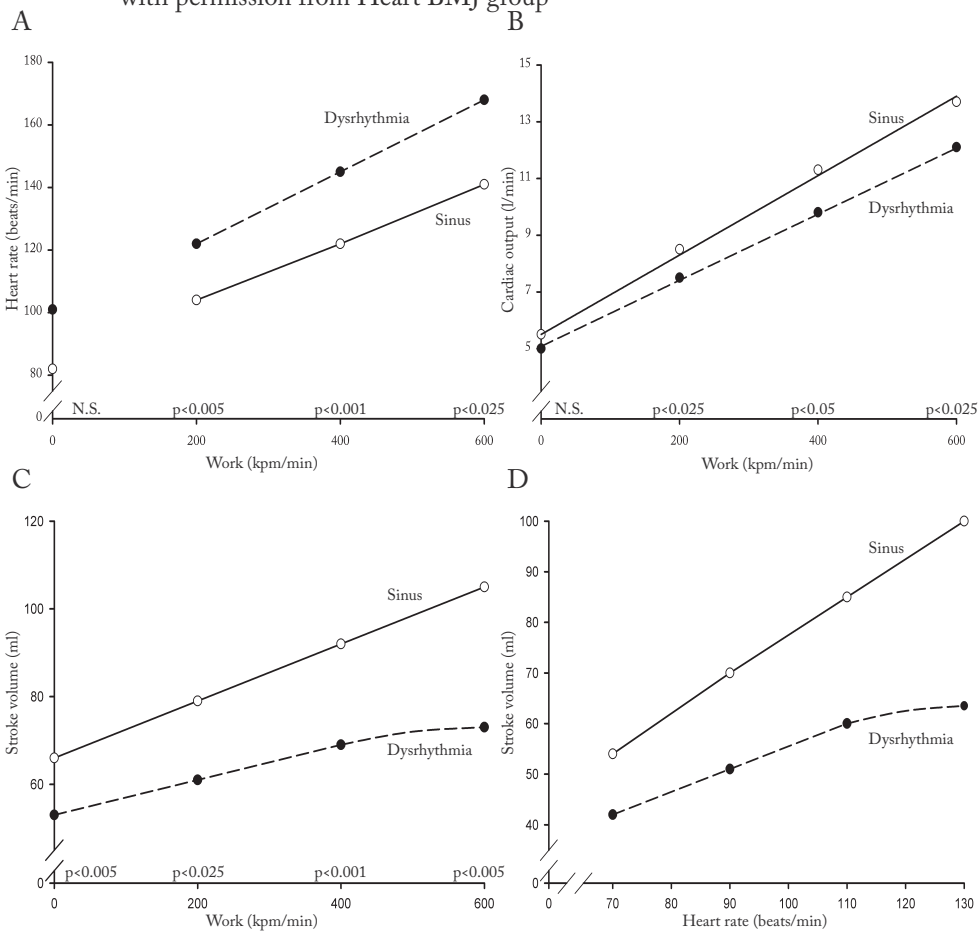
Rate control is the cornerstone of the treatment of AF. The current prevalence of AF in the Netherlands is 5.5%.[15] It is expected that this will double in the next 30 to 50 years.[16,17] Therefore, to be able to keep the treatment of patients with AF manageable a rate control strategy is indispensable. The indifference between rate and rhythm control in terms of cardiovascular morbidity, mortality and quality of life was shown by the Pharmacological Intervention in Atrial Fibrillation (PIAF), the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE), the Strategies of Treatment of Atrial Fibrillation (STAF), the How to Treat Chronic Atrial Fibrillation (HOT CAFE), and the Japanese Rhythm Management Trials for Atrial Fibrillation (JRhythm).[18-25] After these trials, rate control had become therapy of choice in older patients without severe symptoms. There were, however, some differences in rate control strategies used in the trials which investigated the outcomes between rate and rhythm control. Therefore, the optimal level of rate control was still unknown.[26] In addition, there were no prospective data on rate control and outcome in permanent AF.

Institution of Rate Control in Atrial Fibrillation

The ventricular rate during AF is determined by the conduction characteristics of the atrioventricular node, and activity of the sympathetic and parasympathetic tonus. Negative dromotropic drugs can be used to lower the ventricular rate during AF. Three types of drugs are commonly used: beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin. They can be used alone or in combination with each other. Beta-blockers reduce the ventricular frequency due to blockade of the sympathetic activity (ß1-receptor) in the atrioventricular node. Nondihydropyridine calcium-channel blockers slow the atrioventricular node by increasing the refractory period of the atrioventricular node due to blockade of calcium channels. Digoxin exhibits its function through increase of the parasympathetic tonus, and thereby reducing the atrioventricular conductance. Therefore, digoxin is not the most appropriate drug in patients with a high sympathetic drive i.e., physically active or critically ill patients.

Common side effects of beta-blockers include cold extremities, bronchoconstriction, impotence, and fatigue. The first two comprise relative contraindications for beta-blocker use in patients with peripheral vascular disease and pulmonary disease, respectively. Constipation is one major side effect associated with the use of nondihydropyridine calcium-channel blockers, and therefore this drug is not suitable for patients with constipation. In addition, peripheral edema is also a major side effect of nondihydropyridine calcium-channel blockers. Digoxin is a reasonable drug for older patients who are physically inactive. Sotalol, a beta-blocker with additional class III anti-arrhythmic effects, can also be used as a rate control drug.[27,28] However, the additional class III effects induce QT-prolongation and may cause life threatening arrhythmias, i.e. torsades de pointes. Therefore, sotalol is not recommended for rate control.[29-32] Dronedarone also has negative dromotropic characteristics.[33]

Figure 1. Hemodynamic changes during AF, adapted from Resnekov and colleagues,[44] with permission from Heart BMJ group



However, dronedarone may increase the risk of stroke, heart failure, and cardiovascular death in patients with permanent AF and major risk factors for cardiovascular events. Therefore, dronedarone is contraindicated for rate control.[34] Amiodarone is another alternative to reduce heart rate.[35] However, due to its extensive (non cardiac) adverse effects it remains restricted to a small subset of patients,[36-38] i.e. critically ill patients and those with (acute) heart failure in whom beta-blockers and digoxin are insufficient to reduce the heart rate adequately.[39] As last resort therapy pacemaker implantation in combination with atrioventricular node ablation can be performed in patients in whom the heart rate cannot be reduced with drugs or in whom drugs induce severe adverse effects necessitating discontinuation.[40] However, right ventricular pacing can induce heart failure.[41,42] Cardiac resynchronization therapy may therefore be the pacing mode of choice after atrioventricular node ablation.[43]

What is the optimal heart rate during AF? The previous guidelines recommended a resting heart rate between 60 and 80 beats per minute, and between 90 and 115 beats per minute during moderate exercise.[1] However, these recommendations were not based on prospective randomized trials investigating different rate control strategies. On the contrary, they were based on two small scale studies. The first study was performed in 60 patients with AF, and conclusions were based on a mathematical model on flow velocity in the ascending aorta and resting heart rate.[14] In each individual patient the ventricular rate was calculated for the maximal cardiac output. In the entire group the maximal cardiac output was achieved at a mean heart rate of 122 beats per minute. In 16 patients the resting heart rate was higher than the calculated heart rate for maximum cardiac output. All these patients had a resting heart rate above 90 beats per minute. The second study on the basis of which former guidelines advocated a strict rate control strategy assessed hemodynamic parameters in 6 patients before and after electrical cardioversion.[44] The investigators observed a higher heart rate (Figure 1A), and lower cardiac output (Figure 1B) and stroke volume (Figure 1C) when the patients were in AF. The beneficial effect of sinus rhythm was well illustrated when stroke volume was plotted against heart rate (Figure 1D). The investigators concluded that a hemodynamic disadvantage was present during AF. These data, however, do not imply that patients in AF should have a heart rate comparable to patients in sinus rhythm. In contrast, it is possible that during AF patients may benefit from higher heart rates than during sinus rhythm. This is illustrated in Figure 1B. Despite the presence of AF, cardiac output is comparable; the loss in stroke volume during AF is compensated by an increase in heart rate.

Success of Rate Control Drugs

As stated in the previous guidelines, it was a therapeutic goal to reduce the heart rate during AF to a level comparable to the heart rate during sinus rhythm.[1] Therefore, from the 1970's, throughout the first decade of the 21st century, studies were performed evaluating negative dromotropic drugs in patients with AF (Table 1).[28,33,45-55,55-58,58-83]

However, the numerous trials do not represent a homogeneous patient group. For instance, Joglar and colleagues performed an analysis of the effect of carvedilol in patients with AF and a left ventricular ejection fraction <35%. In contrast, Farshi and colleagues included only patients with AF and a left ventricular ejection fraction >35%. Furthermore, the outcome parameters used in the studies were not always comparable. Some of the trials used resting heart rate,[45,48] others used the mean heart rate during 24 hour Holter monitoring.[33,50] In addition, follow-up duration differed from 1 day to 6 months. Despite a reduction of heart rate, rate control strategies do not banish the negative effects of AF, i.e. the loss of atrial kick and ventricular irregularity.[10] Furthermore, it remained uncertain which rate control drug was the most effective. It also remained unclear which patient has the largest advantage of which drug. Farshi and colleagues performed a comparison of 5 drug regiments on the mean 24-hour heart-rates, circadian patterns, and ventricular response on exercise in 12 patients with permanent AF.[50] The drug regiments consisted of digoxin, diltiazem, atenolol, digoxin and diltiazem, and digoxin and atenolol. The most effective treatment, i.e. treatment with the lowest heart rate, was the combination of atenolol and digoxin, reflecting the combined effect of these negative dromotropic drugs on the atrioventricular node. However, the dose of atenolol was not very high (50 mg/day). It is possible that a dose of 100 mg atenolol per day is more effective than the regiments used in the study of Farshi and colleagues. The efficacy of rate control drugs was also evaluated in AFFIRM trial.[2] The rate control criteria used in AFFIRM were a resting heart rate ≤80 beats per minute, and ≤110 beats per minute during moderate exercise. In addition, on Holter a mean HR ≤100 beats per minute, and not >110% of the maximum predicted heart rate.[84] In this post-hoc analysis of the AFFIRM all patients randomized to the rate control group were included. The data of 2027 patients were evaluated. In 58% of patients adequate rate control was achieved with the first drug or combination of drugs. A change or addition was required in 37% of patients, 23% switched from calcium-channel blockers to beta-blockers, 19% changed from beta-blockers to calcium-channel blockers, and 34% started either a beta-blocker or calcium-channel blocker, when they were already using digoxin. In the RACE II study only 25% of patients used ≥2 rate control drugs at baseline (Figure 2). After the dose adjustment phase 35% of patients required ≥2 more rate control drugs in the lenient group, as compared to 68% in the strict rate control group (**chapter 3**). The AFFIRM investigators concluded from their analysis that beta-blockers were most effective in controlling heart rate. There were, however, frequent medication changes necessary to achieve the strict rate control criteria as defined in the AFFIRM trial (Figure 3). Eventually the rate control criteria were achieved in 68% of patients. It is important to consider that in AFFIRM also patients with paroxysmal AF were included. This means that not all patients were in AF during the complete follow-up period. At baseline, 48% of the patients were in AF; this was 42, 44, and 51% at 1, 3 and 5 years follow-up, respectively.[2] In RACE II, however, over 90% of patients were in AF during follow-up (Figure 4). In RACE II, 67% of patients randomized to

Table 1. Heart rate control assessment with negative dromotropic drugs

Study	Design	Drugs	Number of patients	Type of AF Patients
Beta-blocker versus placebo				
Lundström, 1992[46]	Randomized double blind crossover study	Xametorol vs. verapamil vs. placebo	21	Permanent AF
Atwood, 1999[47]	Randomized crossover study	Betaxolol vs. placebo	12	Permanent AF
Joglar, 2001[48]	Randomized placebo controlled, double blind retrospective analysis	Carvedilol vs. placebo	136	AF and heart failure
Kochiadakis, 2001[29]	Randomized, crossover, single blind	Metoprolol vs. sotalol vs. placebo	23	Permanent AF
Beta-blocker versus digoxin				
Yahalom, 1977[61]	Open label clinical trial	Digoxin vs. digoxin + practolol	28	Permanent AF
Khalsa, 1978[60] †	Open label clinical trial	Digoxin + metoprolol 50 vs. digoxin + metoprolol 100	NA	Permanent AF
David, 1979[62]	Open label crossover study	Digoxin vs. digoxin + timolol	28	Permanent AF
DiBianco, 1984[63]	Randomized double-blind crossover study	Digoxin vs. digoxin + nadolol	20	Permanent AF
Atwood, 1987[64] †	Randomized double-blind crossover study	Digoxin vs. digoxin + celiprolol	9	Permanent AF
Ang, 1990[65]	Randomized crossover study	Digoxin vs. xamoterol	13	Permanent AF
Channer, 1994[66]	Randomized single blind cross over study	Digoxin + atenolol vs. digoxin + pindolol	8	Permanent AF
Lawson, 1995[67] †	Randomized double blind crossover study	Xamoterol vs. xamoterol + digoxin vs. digoxin	20	Permanent AF
Lanas, 1995[49]	Randomized double blind crossover study	Digoxin versus atenolol	13	Permanent AF
Koh, 1995[58]	Randomized, cross over	Control vs. betaxolol + digoxin vs. diltiazem + digoxin	45	Permanent AF

AF= atrial fibrillation; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association.

Follow-up	Endpoint	Results - Heart rate	Results - Exercise time or LVEF
2 weeks	Resting HR, exercise HR	HR decreased with both	No improvement of exercise capacity
n.a.	HR rest and exercise; exercise capacity	Reduction of HR at rest and during exercise	Maximal oxygen uptake reduced with betaxolol
6 months	LVEF	NA	LVEF improved with carvedilol
4 weeks	Mean HR; HR during exercise	Both lower mean HR compared to placebo; sotalol reduced HR more during moderate exercise	NA
2 - hours	Resting HR, exercise HR	Resting and exercise HR was lower with digoxin + practolol	NA
NA	Resting HR, exercise HR	Resting and exercise HR was lower with digoxin + metoprolol	NA
4-18 months	Resting HR, exercise HR	Resting and exercise HR lower with digoxin + timolol	NA
8 weeks	Resting HR, exercise HR	Resting and exercise HR was lower with digoxin + nadolol	No increase in exercise capacity
NA	Resting HR, exercise HR	Lower resting and exercise HR	Celiprolol reduces exercise capacity
2 weeks	Resting HR, exercise HR	Resting HR lower with digoxin, exercise HR lower with xametorol	No differences in exercise time were observed
2 weeks	Minimum and maximum HR	Digoxin + pindolol increases nocturnal HR, digoxin + atenolol decreases the nocturnal HR	NA
1 month	Walking distance 6MWT	Xamoterol and digoxin lowerd mean daytime HR	Walking distance improved during xamoterol treatment
2 weeks	Resting HR; exercise HR exercise capacity; symptoms	Resting HR similar; HR at maximal exercise lower	Exercise time longer with atenolol
4 weeks	Resting HR; HR during exercise; exercise capacity	Resting HR more reduced with betaxolol	Exercise capacity improved in both compared to control

AF= atrial fibrillation; HR= heart rate; LVEF = left ventricular ejection fraction; 6 MWT= 6 min walking test

Table 1. Heart rate control assessment with negative dromotropic drugs (continued)

Study	Design	Drugs	Number of patients	Type of AF Patients
Farshi, 1999[50]	Randomized cross over	Digoxin vs. diltiazem vs. atenolol vs. digoxin + diltiazem vs. digoxin + atenolol	12	Permanent AF LVEF >35% NYHA I/ II
Khand, 2003[51]	Randomized, controlled, double blind	Digoxin vs. digoxin + carvedilol	47	AF> 1 month LVEF <40%
Calcium channel blocker versus placebo				
Lewis, 1987[67] †	Open label cross over	Verapamil	12	Permanent AF
Lewis, 1988[58] †	Open label cross over	Digoxin vs. verapamil vs.diltiazem, alone and in combination	6	Permanent AF
Atwood, 1988[53]	Open label clinical trial	Diltiazem vs. control	9	Permanent AF
Lundström, 1990[54]	Randomized, placebo controlled	Diltiazem vs. verapamil vs. placebo	18	Permanent AF
Calcium channel blocker versus digoxin				
Klein, 1979[68] †	Open label clinical trial	Digoxin vs. digoxin + verapamil	23	Permanent AF
Waxman, 1981[69] †	Randomized double-blind crossover study	Digoxin vs. digoxin + verapamil	20	Permanent AF
Stern, 1982[70]	Randomized double-blind crossover study	Digoxin vs. digoxin + verapamil	9	Permanent AF
Panidis, 1983[71]	Randomized double-blind crossover study	Digoxin vs. digoxin + verapamil	27	Permanent AF
Lang, 1983[55]	Open label cross over study	Verapamil vs. digoxin	52	Permanent AF
Lang, 1983[55]	Double-blind crossover study	Digoxin vs. digoxin + verapamil	20	Permanent AF
Roth, 1986[73]	Open label clinical trial	Digoxin vs. diltiazem vs. digoxin + diltiazem	12	Permanent AF
Myers, 1987[74]	Randomized double-blind study	Digoxin vs. digoxin + celiprolol vs. digoxin + diltiazem	9	Permanent AF

AF= atrial fibrillation; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association.

Follow-up	Endpoint	Results - Heart rate	Results - Exercise time or LVEF
2 weeks	Mean HR; HR during exercise	Digoxin + atenolol most effective for mean 24-hour HR and exercise HR	NA
6 months	HR LVEF NYHA class	Digoxin+carvedilol lowered mean HR and submaximal exercise; improved symptoms	Improved LVEF; 6 MWT unaltered and not different
6 weeks	Exercise HR	Exercise HR lower with verapamil treatment	No improvement of exercise capacity
1 day	Resting HR; HR during exercise; exercise tolerance; cardiac output	Best reduction exercise HR by digoxin + diltiazem	No difference in exercise capacity or cardiac output
1 week	Resting HR; exercise HR; Exercise capacity	Diltiazem reduced resting HR and exercise HR.	No differences in exercise capacity
NA	Mean HR; Exercise tolerance	Verapamil and diltiazem decreased HR	Modest improvement of exercise tolerance
NA	Resting HR, exercise HR	Digoxin and verapamil reduce HR response during exercise	NA
NA	Resting HR	Resting HR is lower with digoxin + verapamil	NA
2 weeks	Resting HR, exercise HR	Resting and peak exercise HR was lower with digoxin + verapamil	NA
2 weeks	Resting HR, exercise HR	Resting and exercise HR lower with digoxin +verapamil	NA
4 months	Exercise HR	Verapamil reduced resting HR and HR during execise	Verapamil increased exercise capacity
4 weeks	Resting HR, exercise HR	Resting and peak exercise HR was lower with digoxin + verapamil	NA
4 weeks	Resting HR, exercise HR	Resting and exercise HR was lower with digoxin + diltiazem	NA
4 weeks	Resting HR, exercise HR exercise capacity	Lower resting and exercise HR with digoxin + celiprolol or + diltiazem	Digoxin + celiprolol reduced VO2 at maximum exercise

HR= heart rate; LVEF = left ventricular ejection fraction; 6 MWT= 6 min walking test

Table 1. Heart rate control assessment with negative dromotropic drugs (continued)

Study	Design	Drugs	Number of patients	Type of AF Patients
Steinberg, 1987[75] †	Open label clinical trial	Digoxin vs. digoxin + diltiazem	16	Permanent AF
Atwood, 1988[53]	Open label clinical trial	Digoxin vs. digoxin + diltiazem	9	Permanent AF
Maragno, 1988[76]	Open label clinical trial	Digoxin vs. diltiazem vs. digoxin + diltiazem	19	Permanent AF
Pomfret, 1988[77] †	Double blind placebo controlled study	Digoxin vs. verapamil vs digoxin + verapamil	8	Permanent AF
Lewis, 1988[58] †	Open label clinical trial	Digoxin vs. digoxin + verapamil vs. digoxin + diltiazem	6	Permanent AF
Lewis, 1988[53]	Randomized double blind crossover study	Digoxin, diltiazem and digoxin + diltiazem	14	Permanent AF
James, 1989[78] †	Randomized crossover study	Digoxin vs. digoxin + pindolol vs. digoxin + verapamil	12	Permanent AF
Wong, 1990[79]	Randomized double-blind crossover study	Digoxin vs. labetolol vs. digoxin + labetolol	10	Permanent AF
Lundstrom, 1990[54] †	Open label clinical trial	Diltiazem vs. verapamil	18	Permanent AF
Gupta, 1992[80] †	Open label clinical trial	Digoxin vs. digoxin + diltiazem	20	Permanent AF
Dahlström, 1992[81]	Randomized double-blind crossover study	Digoxin vs. digoxin + diltiazem vs. digoxin + propranolol vs. digoxin + diltiazem + propranolol	13	Permanent AF
Koh, 1995[49]	Randomized open label study	Digoxin vs. betaxolol + digoxin vs. diltiazem + digoxin	45	Permanent AF
Botto, 1998[56]	Randomized crossover study	Gallopamil vs. diltiazem vs. verapamil vs. digoxin	18	Permanent AF
Farshi, 1999[50]	Randomized cross over	Digoxin vs. diltiazem vs. atenolol vs. digoxin + diltiazem vs. digoxin + atenolol	12	Permanent AF LVEF >35% NYHA I/ II

AF= atrial fibrillation

Follow-up	Endpoint	Results - Heart rate	Results - Exercise time or LVEF
NA	Resting HR, exercise HR	Lower resting and exercise HR with digoxin + diltiazem	NA
1 week	Resting HR, exercise HR, Exercise capacity	Resting HR and exercise HR lower with digoxin + diltiazem	No differences in exercise capacity
2 weeks	Resting HR, exercise HR	Resting and exercise HR were lower with digoxin + diltiazem	NA
2 weeks	Resting HR, HR during exercise, LV function	Resting and exercise HR were lower with digoxin + verapamil	No deterioration of LVEF
1 day	Resting HR, exercise HR, and tolerance	Digoxin + diltiazem reduced exercise heart rate the most	No improvement of exercise tolerance
1 day	Resting HR, HR during exercise	Resting HR and HR during exercise lower with combination treatment	No improvement of exercise tolerance
NA	Mean 24 hour HR	Mean 24 hour HR lower with digoxin + pindolol	NA
2 weeks	Resting HR, exercise HR	Peak exercise HR was lower with labetolol (with or without digoxin)	No differences in exercise capacity
NA	Mean HR, exercise capacity	Resting and exercise HR lower with diltiazem and verapamil	Exercise capacity modestly improved
NA	Resting HR, exercise HR	Resting and exercise HR lower with digoxin + diltiazem	No effect on exercise capacity
12 weeks	Resting HR, exercise HR	Resting and exercise HR were lower with the combination treatments	No improvement of exercise capacity
4 weeks	Resting HR, exercise capacity	Digoxin + betaxolol and digoxin + diltiazem reduce resting and exercise HR more effectively	No effect on exercise capacity
1 week	HR during exercise	Gallopamil, diltiazem and verapamil superior for rate control	NA
2 weeks	Mean HR; HR during exercise	Digoxin + atenolol most effective for mean 24-hour HR and exercise; Digoxin and diltiazem least effective	NA

AF= atrial fibrillation; HR= heart rate; LVEF = left ventricular ejection fraction; 6 MWT= 6 min walking test; NYHA= New York Heart Association.

Table 1. Heart rate control assessment with negative dromotropic drugs (continued)

Study	Design	Drugs	Number of patients	Type of AF Patients
Digoxin versus amiodaron				
Tse, 2001[35]	Randomized controlled double-blind study	Digoxin vs. amiodaron	16	Permanent AF
Digoxin versus sotalol and placebo				
Brodsky, 1994[27]	Randomized double blind study	Digoxin vs. digoxin + sotalol	60	Permanent AF
Digoxin versus beta-blocker versus calcium channel blocker				
Matsuda, 1991[82] †	Open label clinical trial	Digoxin vs. propranolol vs. verapamil	10	Permanent AF
Lewis, 1989[83] †	Randomized crossover study	Digoxin vs. digoxin + atenolol vs. digoxin + verapamil vs. digoxin + xametorol	NA	Permanent AF
Dronedarone versus placebo				
Davy, 2008[33]	Randomized controlled trial	Drondarone vs. placebo on top of rate control medication	174	Permanent AF >6 months, symptoms

AF= atrial fibrillation; HR= heart rate; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association.

strict rate control had adequate rate control at the end of the dose-adjustment phase, (**chapter 3 and 4**) which is comparable to the AFFIRM. However, as mentioned above, more patients in AFFIRM were in sinus rhythm. Since heart rate is lower in patients in sinus rhythm, as compared to patients in AF, the achievement of the strict rate control criteria in RACE II may be considered even more successful as compared to AFFIRM.

Rate Control and Outcome

Most importantly, what is the effect of heart rate and rate control strategies on outcome? A subanalysis of AFFIRM evaluated the effect of intensity of rate control on outcome.[85] In this study patients randomized to the rate control arm of AFFIRM who were in AF at baseline and at 2 months follow-up were included. The patients were stratified according to the quartiles of resting heart rate at 2 months. There was no difference in outcome between the quartiles of resting heart rate. RACE II was the first prospective randomized clinical trial evaluating the effect of two different rate control strategies on outcome. In RACE II we observed that lenient rate control was non-inferior as compared to strict rate control in terms of cardiovascular morbidity

Follow-up	Endpoint	Results - Heart rate	Results - Exercise time or LVEF
24 weeks	Mean HR Exercise capacity	Similar effect of digoxin and amiodaron on mean HR	Both less effective during exercise
4 weeks	Resting HR, exercise HR	Resting and exercise HR were lower with digoxin + sotalol	NA
1 day	Resting HR, exercise HR	Resting HR and exercise HR were lower with propranolol and digoxin	No difference in oxygen uptake
4 weeks	Exercise HR and tolerance	Exercise HR lower with digoxin + atenolol, verapamil or xametorol	Atenolol and xametorol reduced exercise tolerance
6 months	Mean HR	Reduction of mean HR and at maximal exercise with dronadarone	NA

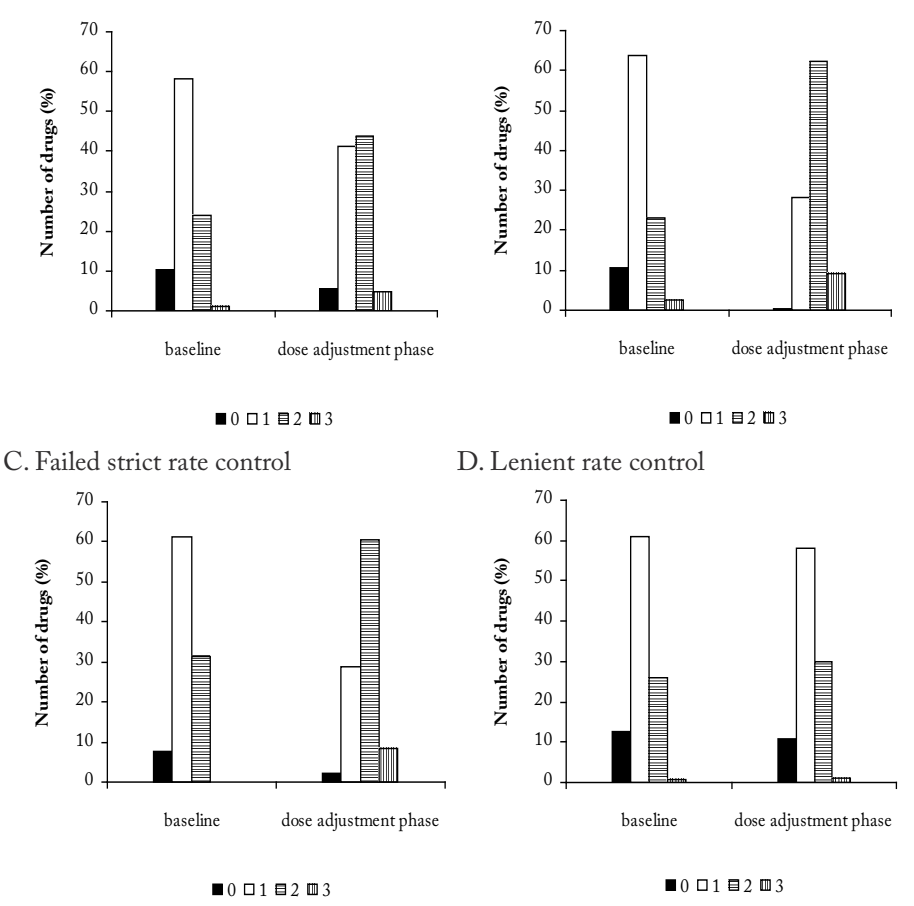
AF= atrial fibrillation; HR= heart rate; LVEF = left ventricular ejection fraction; 6 MWT= 6 min walking test; NYHA= New York Heart Association.

and mortality (**chapter 3**). This outcome led to changes in all AF guidelines and it changed treatment strategies.[16,86,87]

However, strict rate control is difficult to achieve, as was observed in the AFFIRM.[2] This was also observed in RACE II (**chapter 3 and 4**). The failure of strict rate control may have influenced outcome of RACE II, in favor of lenient rate control. Nevertheless, there was also no difference in outcome between successful strict, failed strict, and lenient rate control (**chapter 4**). Thus, the non-inferiority of lenient rate control compared to strict rate control is not a consequence of failure of strict rate control.

We also assessed all-cause mortality and cardiovascular hospitalizations in RACE II. There was no difference between lenient and strict rate control regarding all-cause mortality and cardiovascular hospitalizations (**chapter 6**). This may seem of less importance, but this is not the case. The ideal outcome parameter to assess differences in treatment strategies is all-cause mortality. However, due to the relative good prognosis of patients with AF nowadays (Figure 5), a large number of patients would be required to assess possible treatment differences. One way to overcome this is by using composite endpoints, as was done in RACE II, or by using a surrogate

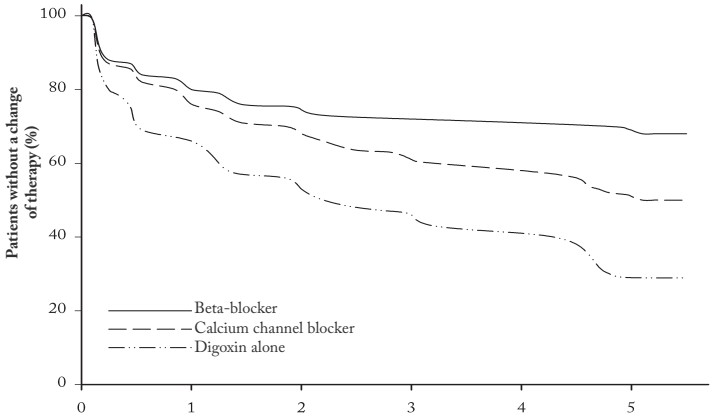
Figure 2. Number of rate control drugs in RACE II



endpoint. A good surrogate endpoint should occur sooner and more frequently than the true endpoint, and is easy to detect.[88] In addition, there should be an association between the surrogate and the true endpoint.[89,90] Cardiovascular hospitalization is a good surrogate endpoint for all-cause mortality.[88,91,92] Thus the equality in all-cause mortality and cardiovascular hospitalization of the two treatment strategies in RACE II adds to the recommendations to start treatment in patients with permanent AF using a lenient rate control strategy (**chapter 6**).

In a retrospective analysis of the patients randomized to rate control in the first RACE trial there was no difference in outcome between patients with a low (<80 beats per minute) versus high (≥80 beats per minute) heart rate (**chapter 2**). Previously, a pooled analysis of AFFIRM and RACE also showed no difference in outcome

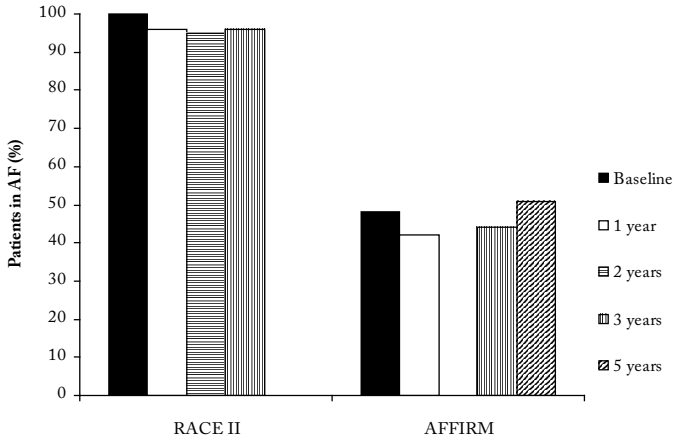
Figure 3. Time to change in rate control therapy, adapted from Olshansky and colleagues,[2] with permission of Elsevier



No. of patients, events (%)						
Beta-blocker	777, 0 (100)	598, 147 (81)	500, 191 (75)	315, 210 (71)	164, 213 (70)	35, 216 (68)
Calcium blocker	631, 0 (100)	461, 139 (77)	379, 167 (69)	246, 220 (62)	128, 238 (56)	20, 247 (48)
Digoxin	315, 0 (100)	190, 104 (66)	142, 140 (53)	92, 160 (45)	43, 165 (42)	5, 172 (29)

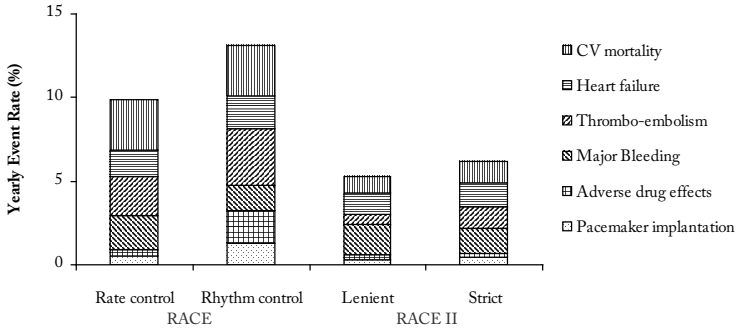
between patients treated with the intention to obtain a higher (< 100 bpm in RACE) and a lower heart rate (<80 bpm in AFFIRM).[93] In that study patients were included if they met a combination of overlapping in- and exclusion criteria of AFFIRM and RACE. The primary endpoint was a composite of all-cause mortality, cardiovascular hospitalization, and myocardial infarction. In total, 1091 patients were included, 874 from AFFIRM and 217 from RACE. The mean heart rate in the AFFIRM patients was lower compared to the patients from RACE due to different rate control

Figure 4. Percentage of patients in AF during follow-up in RACE II and AFFIRM



No data available on percentage of patients in AF at 3 years in AFFIRM

Figure 5. Cumulative incidence of cardiovascular morbidity and mortality in patients with AF



CV mortality - cardiovascular mortality

definitions (76.1 versus 83.4 beats per minute). There was no difference in outcome between the patients included in AFFIRM or RACE. However, a mean heart rate >100 beats per minute was associated with a worse outcome. In RACE II there was no association between heart rate after the dose-adjustment phase and outcome. The difference in heart rate between the lenient and strict group was also larger (93 versus 76 beats per minute, respectively) as compared to the difference between the patients included in AFFIRM and RACE. Furthermore, in the lenient group more than 60% of patients had a heart rate >90 beats per minute, while only a limited number of patients had a heart rate >100 beats per minute (**chapter 3**).

In AFFIRM digoxin use at 2 months was associated with higher all-cause mortality.[85] In the patients randomized to rate control in the RACE study there was also an association between a worse outcome and use of digoxin (**chapter 2**). In contrast, in RACE II there was no association between digoxin and cardiovascular morbidity and mortality, nor was there a relation between the individual components of the primary outcome and digoxin use (**chapter 3 and 4**). In a pooled post-hoc analysis of AFFIRM and RACE, which was mentioned above, there was also no association between digoxin use and a worse outcome.[93] Therefore, no definite conclusions can be made whether digoxin affects outcome in patients with AF. However, considering the risk of digoxin intoxication, it should be used with care in elderly patients and in patients with renal failure.

Patients require different drugs and dosing regiments for rate control, as can be observed in daily clinical practice, and in the aforementioned studies. This is possibly due to differences in body size, liver and renal function, and differences in the atrioventricular-conduction system (i.e., frailty in older patients), which is commonly seen in patients with permanent AF. Thus, institution of rate control is a strategy which requires a patient tailored approach and should be titrated depending on symptoms and the development or deterioration of heart failure. As has been demonstrated in this thesis, a lenient rate control therapy approach is reasonable. In addition, it reminds us to treat the patients, not the electrocardiogram.[94]

Rate Control in Atrial Fibrillation and Heart Failure

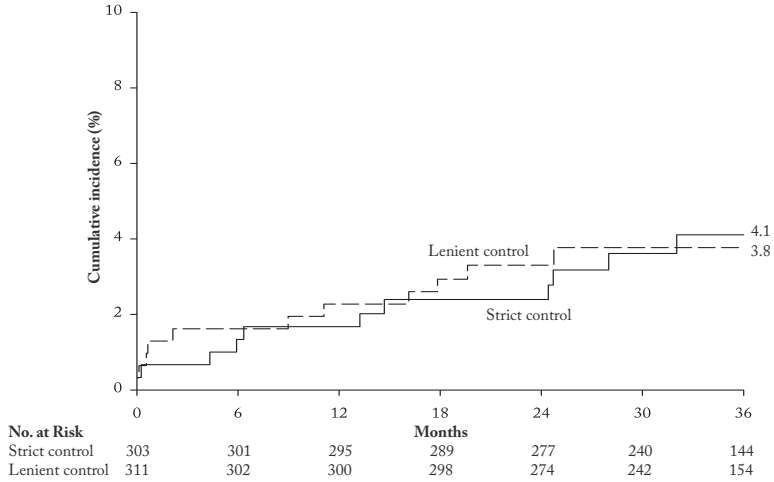
Heart failure and AF often coincide, and the incidence of AF increases with the severity of heart failure.[95,96] AF may deteriorate prognosis in patients with AF, especially in patients with recent onset AF, although this association is not fully elucidated yet.[95,97-106] There may be differences in outcome depending on whether patients hospitalized for AF and heart failure had developed AF or heart failure first.[107] Considering the high incidence of coexisting AF and heart failure, the AFFIRM and RACE did not yet elucidate the rate versus rhythm issue in patients with AF and heart failure. Both studies included a relative low number of patients with heart failure.[18,20] A predefined substudy of RACE assessed all heart failure patients in New York Heart Association functional class II and III.[108] Fractional shortening was comparable between the rate (29±10) and rhythm control (28±9) groups. There was no difference in the incidence of the primary outcome between rate and rhythm control (29% versus 32%, respectively). The first prospective study on outcome in rate versus rhythm control in AF and heart failure was the Atrial Fibrillation and Congestive Heart Failure (AF-CHF). This study showed that, also in patients with AF and heart failure, rate control is non-inferior as compared to rhythm control.[109] In the AF-CHF patients with an ejection fraction <35%, symptoms of heart failure, and a history of AF were included. A total of 694 patients were randomized to rate control, and 682 patients to rhythm control. The mean left ventricular ejection fraction was 27%. There was no difference in cardiovascular morbidity between the two groups (25% in the rate control versus 27% in the rhythm control group, p=0.59). Therefore, rate control can also be used in patients with heart failure, even more since (non) pharmacological rhythm control outcome is relatively low.[9,110] It is, therefore, unknown whether rate control would also be non-inferior if rhythm control strategies would be more effective. Whether lenient rate control can also be instituted in patients with heart failure is unknown. However, due to the reduced left ventricular function in addition to the adverse hemodynamic effects of AF, patients with heart failure and AF may need a higher heart rate as compared to patients with heart failure and sinus rhythm.

Development of heart failure was one of the presupposed risks of lenient rate control. The development or deterioration of heart failure was not increased in the lenient rate control group in the RACE II (Figure 6 A and B, **chapter 3 and 4**). However, the number of patients included in RACE II with systolic heart failure was limited. Diastolic heart failure was not separately assessed. Since the majority of patients suffered from hypertension as associated disease it may be presumed that a majority of patients in RACE II had diastolic heart failure, and were therefore at risk to develop overt heart failure. Our data, nevertheless, suggest that a heart rate just below 110 beats per minute is low enough to prevent patients from developing heart failure in the group of patients included.

There are several retrospective post-hoc analyses on heart rate in patients with AF and heart failure. Rienstra and colleagues evaluated the effect of heart rate in a cohort of patients with AF and heart failure.[111] In this post-hoc analysis of the Second Prospective Randomized Study of Ibopamine on Mortality and

Figure 6. Cumulative incidence of hospitalizations for heart failure in RACE II

A - According to lenient and strict rate control



No. at Risk							
Strict control	303	301	295	289	277	240	144
Lenient control	311	302	300	298	274	242	154

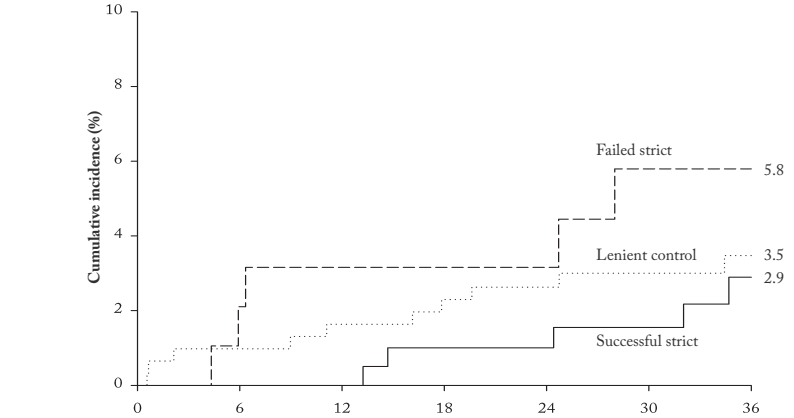
Efficacy (PRIME II) 77 patients were included.[112] PRIME II was a survival study on ibopamine in patients with severe heart failure. Mean left ventricular ejection fraction was 23%. The investigators found no differences between patients with a lower (≤80 beats per minute) and a higher (>80 beats per minute) baseline heart rate. In contrast to what was expected, a low heart rate was independently associated with all-cause mortality in this study. However, this was a retrospective study including a very limited number of patients and no data were available on heart rate during follow-up. Furthermore, at the time of PRIME II, beta-blockers were only rarely instituted in heart failure. In the cohort of Rienstra and colleagues only 6.5% of patients used a beta-blocker.

Despite the proven efficacy of beta-blockers in patients with heart failure and sinus rhythm on survival, the benefit in patients with AF is still unclear.[47,102,113,114] Of 4 major studies on beta-blocker use in heart failure, post-hoc analyses were performed assessing the effect of beta-blockers in patients with AF and heart failure (Table 2).[47,102,115,116] In the post-hoc analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) there was no difference in all-cause mortality between patients in sinus rhythm or in AF. However, the survival benefit of bisoprolol was only present in the patients in sinus rhythm.[115] Furthermore, in the post-hoc analysis of the U.S. Carvedilol Heart Failure Study Group there was no significant difference in outcome between the patients treated with a beta-blocker or placebo.[47] The Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) also showed no survival benefit in the patients with AF who were treated with a beta-blocker, in contrast to the patients in sinus rhythm.[102] In addition, in elderly patients with AF and heart failure, beta-blocker treatment did not improve outcome.[116]

Why do beta-blockers not improve outcome in patients with AF? First, the

Figure 6. Cumulative incidence of hospitalizations for heart failure in RACE II

B - According to successful strict, failed strict and lenient rate control



No. at Risk							
Failed strict	98	93	90	87	82	68	39
Successful strict	203	200	198	195	193	167	99
Lenient control	307	301	299	296	283	272	153

baseline heart rate in all three aforementioned studies was relatively low. It is possible that the additional heart rate reduction does not improve survival in patients with AF. Due to the loss of atrial kick and ventricular irregularity, these patients might require a higher heart rate than patients in sinus rhythm. Second, the place of action in AF is in the atrioventricular node, as compared to the sinus node in patients in sinus rhythm. Therefore, beta-blockers may be less effective and act differently in AF as compared to sinus rhythm. This difference may play a role in the absence of a survival benefit for beta-blockers in patients with AF and heart failure. Third, a low heart rate may be a marker of underlying conduction disturbances, which may reduce prognosis on itself.[111]

Other small scale studies on the efficacy of beta-blocker therapy in patients with AF and heart failure showed an improvement of left ventricular function. There was, however, no effect on survival but these studies were not powered to assess the effect of treatment on survival (Table 2).[51,117-120] Khand and colleagues performed a double blind, parallel-arm study investigating the effects of digoxin alone, carvedilol alone, and the combination of both.[51] This study was performed in 47 patients with heart failure and AF. They concluded that the combination of a beta-blocker and digoxin was more effective than the use of a beta-blocker alone or digoxin alone. Furthermore, left ventricular ejection fraction improved during treatment with the combination of the two drugs. In a retrospective observational cohort, Fauchier and colleagues evaluated the effect of beta-blockers and digoxin in 1,269 patients with heart failure and AF. In their cohort 46% of patients had systolic heart failure (left ventricular ejection fraction <45%).[120] In contrast to the post-hoc analysis of the studies on beta-blockers in heart failure, the use of beta-blockers, with or without digoxin, was associated with decreased all-cause mortality compared to no beta-blocker use.

Table 2. Studies on beta-blockers in Atrial Fibrillation and Heart Failure

Study	Number of patients	Age	Male	LVEF	NYHA I/II/III/IV	Ischemic etiology
			(%)	(%)	(%)	(%)
Substudy of RCT on beta-blockers in HF						
Lechat, 2001[115]						
Bisoprolol	257	63	84	27	0/0/80/20	26
Placebo	264	62	82	27	0/0/80/20	25
Joglar, 2001[47]						
Carvedilol	84	66	90	-	0/42/55/4	54
Placebo	52	63	90	-	0/42/56/2	46
Van Veldhuisen, 2006[102]						
Metoprolol CR/XL	274	66	86	28	0/34/167/13	52
Placebo	282	66	87	28	0/34/60/6	55
Mulder, 2012[116]						
Nebivolol	361	77	64	36	2/48/48/2	62
Placebo	377	77	65	36	2/47/46/5	63
Other studies on beta-blockers in AF and HF						
Fung, 2002[118]						
Bisoprolol/ carvedilol	12	64	75	26	0/25/75/0	17
Khand, 2003[51]						
Carvedilol	24	69	58	24	4/46/38/12	33
Placebo	23	68	65	25	4/70/26/0	48
Meng, 2003[119]						
Metoprolol/ carvedilol	24	64	83	33	-	0
Cioffi, 2006[117]						
Carvedilol	39	76	64	31	-	31
Fauchier, 2009[120]						
Beta-blocker	260	73	60	48	-	34
Digoxin	402	76	56	50	-	14

LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; HF - heart failure; HT - hypertension
ACE-i - angiotensin converting enzyme inhibitor

HT	Heart rate	ACE-i	Digoxin	Amiodarone	Outcome
(%)	(%)	(%)	(%)	(%)	
18	85	96	83	18	No change in all-cause mortality
16	90	96	86	18	
-	-	95	100	1	No change in HF hospitalization and
-	-	95	95	2	all-cause mortality, improvement of LVEF
39	85	89	89	-	No change in all-cause mortality
42	84	93	90	-	
64	83	-	-	-	No change in all-cause mortality
60	83	-	-	-	
50	78	92	-	-	Improvement of LVEF, no change exercise capacity
-	89	71	100	-	Improvement of LVEF
-	82	71	100	-	
-	74	88	79	-	Improvement of LVEF
51	82	51	87	-	No change in HF hospitalization
53	-	63	0	29	Digoxin associated with
38	-	80	100	35	worse survival

There was no survival benefit in patients who only used digoxin, compared to the control group (no beta-blocker or digoxin). As mentioned, this was an observational study, and only a third of the patients used a beta-blocker. Furthermore, almost half of the patients in the no-therapy group used anti-arrhythmic drugs, which could have affected outcome.

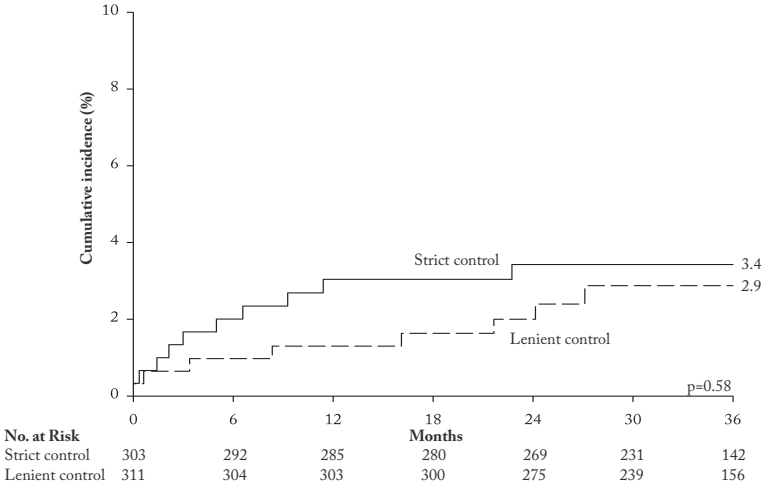
There is one absolute contra-indication for lenient rate control: Cardiac Resynchronization Therapy (CRT). Previously, CRT was only indicated in patients who were in sinus rhythm.[121] However, the present ESC recommendations state that CRT may also be considered in patients with AF and heart failure.[122] There are, however some major issues concerning AF and CRT. The irregular high spontaneous ventricular heart rate reduces the percentage of biventricular pacing. Furthermore, during exercise the ventricular rate can exceed the upper rate of the device,[123] also reducing the amount of biventricular pacing. Therefore, it is essential that when patients with permanent AF receive CRT, they are instituted on a strict rate control strategy, or undergo AV node ablation.[124,125] A strict rate control strategy in AF and heart failure can be instituted with beta-blockers, digoxin, and amiodarone. When the strict approach cannot be achieved with drugs, an atrioventricular node ablation can be performed. Considering the evaluation of the percentage of biventricular pacing, it is essential that this is adequately performed, also when evaluating the success of CRT therapy. Evaluating the parameters supplied by the device is not enough. One of the most simple and cheap methods to evaluate biventricular pacing is with the electrocardiogram. Also an exercise test or 24-hour Holter monitoring can be performed to evaluate the amount of biventricular pacing during exercise.[123] Care for patients with CRT devices should therefore be performed by dedicated cardiologists.

Major Cardiovascular Endpoints in Patients with Atrial Fibrillation

Adequate evaluation of patients with AF is important. Lone AF is not very common, especially not in patients with permanent AF (**chapter 3**). The majority of patients with AF have vascular, valvular, internal or pulmonary disease.[18,20] Prognosis is probably determined by these underlying diseases, rather than by AF.[126,127] During the last decade AF treatment has improved, with a reduction in cardiovascular morbidity and mortality (Figure 6). However, major cardiovascular events still occur in patients with AF.

During the course of the RACE II there was no specific moment on which more endpoints occurred (**chapter 3**). Since the drug-titration phase was a period in which more or new drugs were prescribed to the patients, this may have resulted in more events. This however, was not the case. The arrhythmic events (being syncope, life-threatening adverse effect of rate control drugs, sustained ventricular tachycardia or ventricular fibrillation, cardioverter-defibrillator implantation, and pacemaker implantation) are of special interest during this episode. In the strict rate control group, the endpoints seemed to occur earlier during the study. During the first 12 months, 3 pacemaker implantations, 2 syncopes, and 1 serious adverse event of rate control drugs (hospitalization for AV conduction disturbances) occurred in the strict

Figure 7. Cumulative incidence of arrhythmic events in RACE II



group, as compared to no pacemaker implantations, 2 syncopes and 2 serious adverse events of rate control drugs in the lenient group (Figure 7). This may be caused by the addition or increase of dosages of rate control drugs.

One of the treatment goals of patients with AF is prevention of thromboembolic complications.[16] Risk stratification for these events is essential in all AF patients. The CHA_2DS_2 VASc score is a useful tool to assess the risk of thromboembolic complications in patients with AF.[128] The CHA_2DS_2 VASc score consists of intermediate and high risk factors (Table 3). The maximum score is 9 points, with 0 being low risk patients, 1 intermediate risk, and ≥2 high risk patients. The yearly risk of a thromboembolic complication is 0%, 0.6%, and 3.0%, respectively.[128] The current European guidelines recommend the use of oral anticoagulation in patients with a score ≥2, either aspirin or oral anticoagulation in patients with a score of 1, where oral anticoagulation is preferred, and either aspirin or no antithrombotic therapy in patients with a risk score of 0, where no antithrombotic therapy is preferred.[16] Aspirin is no longer advocated since it increases bleeding risk without reducing the stroke risk.[129] Regardless of the use of oral anticoagulation, stroke and peripheral emboli may occur, even in patients with a low CHA_2DS_2 VASc score.[16,130-132]

In the RACE II the median CHA_2DS_2 VASc score was 2 (interquartile range 1-4). There was no difference between the two randomization groups. Patients with a stroke during the study had a higher CHA_2DS_2 VASc score, compared to patients without a stroke (3, interquartile range 3-4 versus 2, interquartile range 1-4, respectively, p=0.02). The percentage of strokes in RACE II was comparable to The Randomized Evaluation of Long-term Anticoagulation Therapy (RELY) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials. However, follow-up in both these trials

Table 3. CHA_2DS_2-VASc score and HAS BLED score

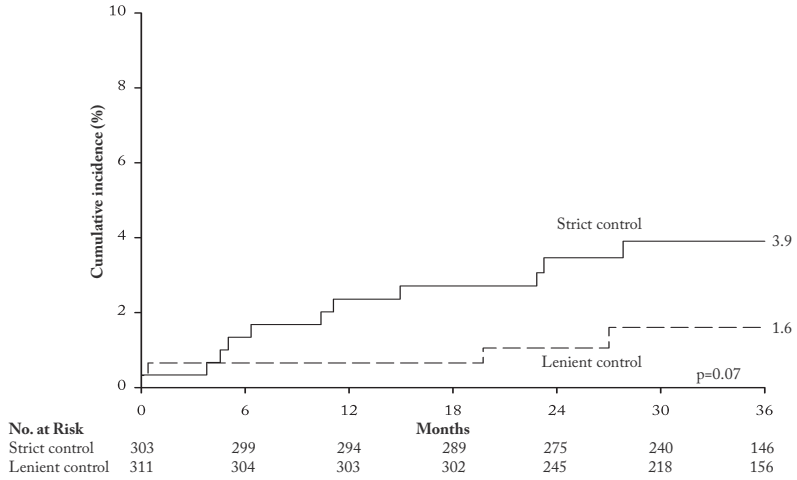
Risk Score	Letter	Clinical characteristic	Points
CHA_2DS_2 VASc[128]	C	Congestive heart failure or left ventricular dysfunction	1
	H	**Hypertension**	**1**
	A	Age ≥75 years	2
	D	Diabetes	1
	S	**Stroke**	**2**
	V	Vascular disease*	1
	A	**Age 65-74 years**	**1**
	Sc	Sex category (female)	1
HAS-BLED[139]	**H**	**Hypertension**	**1**
	A	Abnormal liver of renal function	1 or 2
	S	**Stroke**	**1**
	B	Bleeding	1
	L	Labile INRs	1
	E	**Elderly†**	**1**
	D	Drugs or alcohol	1 or 2

* Vascular disease – previous myocardial infarction, peripheral artery disease, aortic plaque;
† Elderly is defined as an age >65 years;
INR – international normalized ratio

was shorter as compared to RACE II, indicating a higher incidence in RELY and ARISTOTLE. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study the incidence of stroke was higher (Table 4).[18,20,109,130-134] However, the patient cohort in ROCKET-AF was a high risk group with a higher $CHADS_2$ score. Considering the possible instability of the International Normalized Ratio (INR) during the drug-titration phase due to changes in medication, the incidence of strokes could be elevated during this episode. However, there was no indication for an increased stroke incidence during this phase, or any other phase during the study (Figure 8).

It is striking that there seemed to be a trend for a higher incidence of strokes in the strict rate control group of the RACE II study. In 11 patients the INR value was known at the moment of the stroke. In 5 patients with an ischemic stroke the INR was too low. There were 5 hemorrhagic strokes during the study, of which 2 patients had a normal INR, and 1 patient had an elevated INR (3.6). In 2 patients no INR value was available at the moment of the event. Although the numbers were small, there seemed to be no difference in INR values at the moment of the stroke between the lenient and strict groups. There was also no difference in INR between lenient (2.9±0.9) and strict (2.9±0.9) rate control in the patients without a stroke. Considering the higher

Figure 8. Cumulative incidence of stroke in RACE II



incidence of strokes in the strict group, it should be emphasized that RACE II was not powered to make a definite conclusion on this issue.

When instituting oral anticoagulation in patients it is important to assess the bleeding risk.[135,136] Several patient characteristics were associated with increased risk of bleeding and specific bleeding risk scores were developed assessing this major complication of oral anticoagulation.[137-143] The HAS-BLED score is easy to use in daily clinical practice (Table 3).[139] This score was developed using all patients from the Euro Heart Survey of AF with 1-year follow-up status. During the follow-up period 53 (1.5%) major bleeds occurred in the 3456 included patients. The score ranges between 0 and 9, with a score ≥3 implying a high risk of bleeding.[16,139] Patients with a HAS-BLED score ≥3 should therefore be regularly reviewed, and some caution is needed when instituting oral anticoagulation in these patients.

The median HAS-BLED score of the patients in RACE II was 1 (interquartile range 1-2). There was no difference between the two treatment groups. Even in this low risk group of patients bleeding occurred relatively frequent, especially in comparison with the other outcome events in the present population. Fatal bleeding events were uncommon, 3 patients died due to a bleeding (2 intracranial bleedings and 1 retroperitoneal bleeding). The patients with a major bleeding during the study were older (73±5 versus 68±8, $p<0.001$), and had a higher HAS-BLED score as compared to the patients without a bleeding event during the study (2, interquartile range 1-2 versus 1, interquartile range 1-2, respectively, $p=0.04$). The incidence of bleeding events in RACE II was higher as compared to AFFIRM (total of 9.2% in 5 years) and RACE (total of 4% in 2.5 years). At the time of AFFIRM and RACE oral anticoagulation was stopped when patients remained in sinus rhythm, in contrast to RACE II, where patients were continuously treated with oral

Table 4. Patient characteristics of large AF studies

Study	n	Age	Male	Hypertension	Coronary artery disease	Heart failure	Diabetes
		(%)	(%)	(%)	(%)	(%)	(%)
AFFIRM[18]	4,060	70	61	51	26	23	-
RACE[20]	522	68	63	19	10	19	11
AF-CHF[109]	1,376	66	82	48	48	100	21
RACE II[chapter 3]	614	68	66	61	18	10	11
ANDROMEDA[133]	627	71	75	37	65	100	22
ATHENA[134]	4,628	72	53	86	30	21	-
RELY[130]	18,113	72	63	79	17	32	23
ROCKET-AF[131]	14,264	73	60	91	17	62	40
ARISTOTLE[132]	18,201	70	65	87	14	36	25

* Cumulative incidence at end of follow-up
† fractional shortening
# percentage during total follow-up.

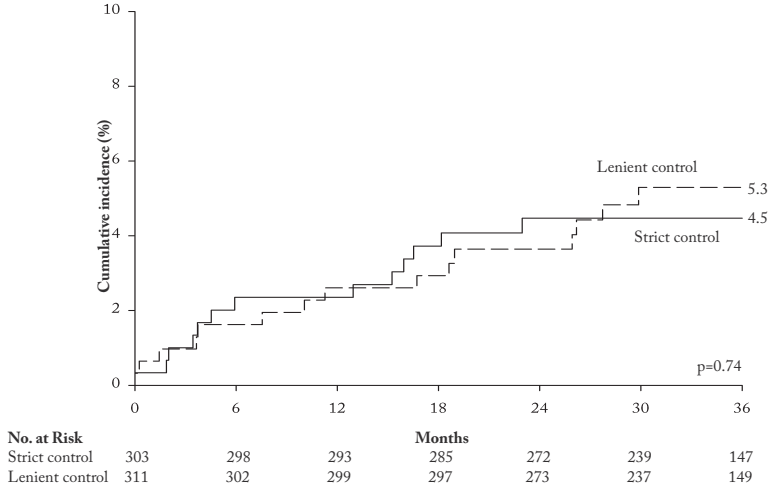
anticoagulation. This may have caused the higher incidence of bleedings in RACE II. The bleeding risk was, however, not as high as in the high risk population of RELY and ROCKET (Table 6).[18,20,130,131] Considering the increased risk of bleeding during the initiation phase of oral anti-coagulation,[144] the additional negative dromotropic drugs, on which the patients were instituted during the dose-adjustment phase, may have influenced the stability of the INR. However, bleedings occurred at similar moments and in similar numbers of patients in both groups (Figure 9).

The incidence of acute coronary syndromes was low in the RACE II, the cumulative incidence in the lenient group being 1.4% (4 patients), as compared to 0.4% (1 patient) in the strict group. There was no difference between the two groups (p=0.2).

Considering the adverse events that occur in patients with AF, it is important that patients with AF are adequately evaluated. A thorough disease specific history and an adequate physical examination should be performed when patients are referred for new onset AF. Thereafter, patients should be instituted on adequate rate control, and, based on their CHA_2DS_2 VASc and HAS-BLED scores, should start with oral anticoagulation. Furthermore, additional diagnostic tests should be performed to exclude any underlying heart disease, for instance heart failure, valve disease or coronary artery disease. The follow-up of AF patients can be performed by a general practitioner, and the patient can be referred to the cardiologist when needed. Future care for patients with newly diagnosed AF may be performed by a nurse specialized in AF. Underlying disease and adequate oral anticoagulation should be the focus of treatment. This may improve guideline adherence, and, subsequently, prognosis. Guideline adherence in the Euro Heart Survey was associated with a reduction of morbidity and mortality.[145] Furthermore, it may reduce costs.[146]

Stroke or TIA	$CHADS_2$	LVEF	Follow-up	Mortality	Stroke	Bleeding
(%)		(%)	yrs	(%)	n (%)	n (%)
-	na	55	3.5	666 (26.3)*	211 (8.2)*	203 (7.3)*
14	1.1±1.0	30†	2.3	40 (6.9)*	35 (6.7)*	21 (4.0)*
10	na	27	3.0	445 (32.5)#	20 (1.5)#	55 (4.0)#
8	1.4±1.1	52	3.0	35 (6.1)*	15 (2.7)*	28 (4.9)*
-	na	-	0.2	37 (6.4)#	7 (5.8)#	-
-	na	-	1.8	255 (5.8)#	-	-
20	2.1±1.1	-	2.0	1371 (7.6)#	478 (2.6)#	1094 (6.0)#
55	3.5±1.0	-	1.9	1214 (8.5)#	429 (3.0)#	781 (5.5)#
20	2.1±1.1	-	1.8	1272 (7.0)#	449 (2.5)#	789 (4.3)#

Figure 9. Cumulative incidence of major bleeding in RACE II



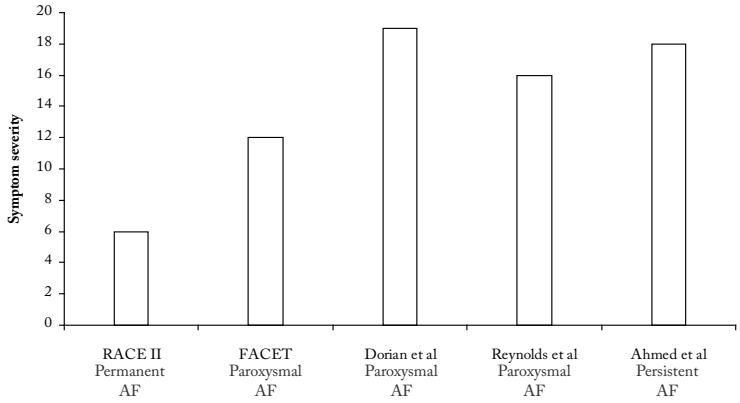
Recently, Hendriks and colleagues showed a reduction in mortality in patients treated in a nurse-led AF clinic.[147] In this study, 111 patients were treated by a specialized nurse, supervised by a cardiologist and supported by a dedicated ICT program. Also, guideline adherence was higher in the AF-clinic patients compared to patients treated by the cardiologist (70% versus 96%, respectively).[148] The effect of treatment in AF-clinics will be studied in RACE 4.

Quality of Life and Symptoms of Atrial Fibrillation

Quality of life is reduced in patients with AF.[25,149] Despite a positive effect of maintenance of sinus rhythm on quality of life, there is no difference in quality of life between rate and rhythm control strategies.[24,25,150,151] The indifference in quality of life between these strategies is probably due the failure of current rhythm control strategies. The hypothesis of the RACE II concerning quality of life was that there would be no difference in quality of life between lenient and strict rate control.[26] Strict rate control may reduce symptoms due to a lower heart rate, but, on the other hand, it may also cause more drug related side effects, resulting in reduced quality of life. A post-hoc analysis of the AFFIRM trial showed no difference in quality of life between the quartiles of resting heart rates.[85] In RACE there was also no difference in quality of life between patients with a lower (rate <80 beats per minute) as compared to patients with a higher (≥80 beats per minute) mean resting heart rate (**chapter 2**). The RACE II showed no effect of the two treatment strategies on quality of life (**chapter 5**). In the RACE II quality of life was assessed with three questionnaires: the Medical Outcome Study Short Form-36 (SF-36) assessed general health related quality of life.[152,153] The University of Toronto AF Severity Scale (AF severity scale) assessed the severity of AF related symptoms, and is AF specific.[149,154,155] The Multidimensional Fatigue Inventory-20 (MFI-20) assessed the severity of fatigue.[156,157] At baseline there were no differences in quality of life between lenient and strict rate control in any of the questionnaires used. Importantly, at one year follow-up, and at end of study there were also no differences in quality of life between lenient and strict rate control, measured with the SF-36, AF severity scale, and the MFI-20 (**chapter 5**). There was also no difference in quality of life between patients with successful or failed strict rate control (**chapter 4**).

How can the absence of a relation between stringency of rate control and quality of life be explained? First, all patients included in the RACE II had permanent AF. The symptoms of patients with permanent AF are different from those with paroxysmal AF and also relate to the age of the patient (**chapter 5**).[158,159] The majority of patients included in RACE II suffered from fatigue and dyspnea, rather than palpitations, which is a major symptom in patients with paroxysmal AF.[160] Symptoms of the patients included in RACE II may be associated with the associated disease, e.g. diastolic dysfunction, rather than the arrhythmia. Therefore, stringency of rate control may have less effect on symptoms, and consequently on the quality of life that the patients experience, as long as the heart rate is not extremely high, e.g. above our lenient rate control target. Furthermore, almost half of the patients included in RACE

Figure 10. Symptom severity measured with the AF severity scale



II had no symptoms of AF. The relative low symptom burden is also reflected in the AF severity scale (Figure 10). Compared to patients with paroxysmal AF (FACET,[157] Dorian and colleagues[149]), persistent AF,[155] and those eligible for catheter ablation (Reynolds and colleagues[161]), patients included in RACE II scored intriguingly low on the AF symptom severity scale. In addition, it seems obvious that symptoms are not affected by different rate control strategies in patients without symptoms, although during any one of the strategies e.g. adverse drug effects may affect symptoms.

There is a significant difference in number of rate control drugs used between the strategies (Figure 2, **chapter 3 and 5**). In addition, the strict rate control strategy required more outpatient department visits (**chapter 5**). This shows that in RACE II two completely different strategies were used. Despite the different strategies, the difference in heart rate was not as marked as would have been expected from the design of the study. However, no difference in quality of life between lenient and strict rate control was observed (**chapter 4 and 5**). It is possible that the positive effects of a lower heart rate during a strict rate control strategy were abolished due to more and higher dosages of rate control drugs with more adverse effects, and more frequent outpatient department visits with additional exercise tests or 24 hour Holter monitoring.

Another explanation why there is no difference in quality of life between lenient and strict rate control could be that patients with failed strict rate control have a lower quality of life than those with successful strict rate control. This could have influenced outcome in favor of lenient rate control. However, there was no difference in quality of life between patients with successful strict or failed strict rate control (**chapter 4 and 5**). Finally, irrespective of a lower or higher heart rate, the ventricular irregularity caused by AF remains, and patients may remain symptomatic due to this irregularity.

Table 5. Recommendations of AF guidelines regarding rate control

Guideline	Heart rate recommendation	Recommendation
ESC Guidelines for the management of AF[16]	It is reasonable to initiate treatment with a lenient rate control protocol aimed at a resting heart rate <110 beats/min	Class IIa, level of evidence B
	It is reasonable to adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control	Class IIa, level of evidence B
ACCF/ AHA/ HRS focused update on AF[87]	Treatment to achieve strict rate control of heart rate is not beneficial compared to achieving a resting heart rate <110 beats/min in patients with persistent AF who have stable ventricular function and no or acceptable symptoms related to the arrhythmia	Class III – No benefit
Canadian Cardiovascular Society AF guidelines: Rate and Rhythm management[86]	We recommend that treatment for rate control of persistent or permanent AF or AFL should aim for a resting heart rate of <100 beats/min	Strong recommendation, high-quality evidence

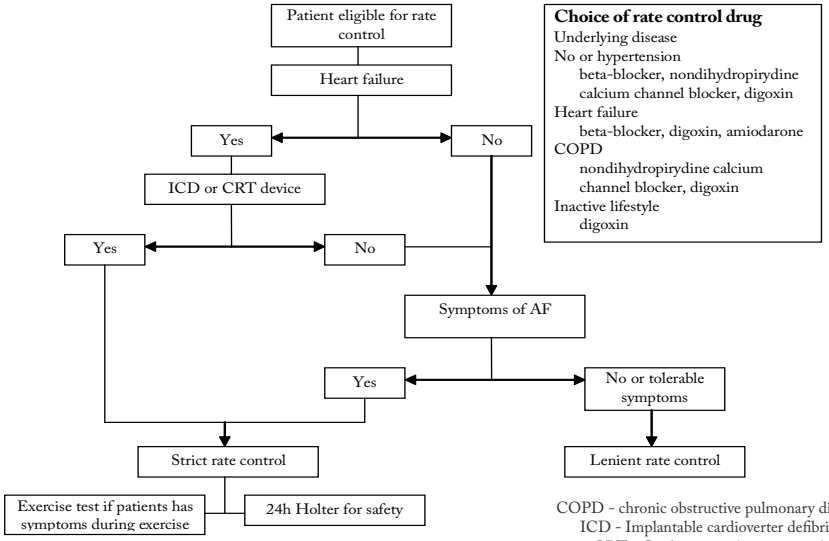
ESC - European Society of Cardiology; ACCF - American College of Cardiology; AHA - American Heart Association; HRS - Heart Rhythm Society; AFL - atrial flutter

Therapeutic implications

After the landmark trials AFFIRM and RACE, rate control has become frontline therapy in older patients without severe AF related symptoms. With the results of the RACE II in hand, we have more evidence that the patient should be treated rather than the ECG.[16,94] The current guidelines have also incorporated the outcome of RACE II in the recommendations regarding rate control. There are, however, some differences in the interpretation and recommendations made in the different guidelines (Table 5).[16,86,87] The American guideline recommends not to use a strict approach in patients with a stable left ventricular function, and acceptable symptoms of AF. The Canadian guideline recommends a rate control strategy with adequate rate control defined as a resting heart rate <100 beats per minute. The major difference between the guidelines is the different heart rate criterion used in the Canadian guideline. This was done because the number of patients with a heart rate >100 beats per minute in RACE II was limited, and therefore the result may not be extrapolated when all patients had a heart rate between 100 and 110 beats per minute. The European guideline advocates to start with a lenient rate control strategy, and when symptoms endure or develop, a stricter rate control strategy can be used.

Considering the above, the outcome of RACE II has simplified treatment of patients with permanent AF. Therefore less outpatient visits are required, which is a benefit for both the patients and the physician.

Figure 11. Flowchart for rate control



COPD - chronic obstructive pulmonary disease;
ICD - Implantable cardioverter defibrillator;
CRT - Cardiac resynchronization therapy;
Modified from Camm and colleagues, Europace 2010[16]

Rate control is adequate when the ventricular rate is <110 beats per minute, and the patient does not have (severe) symptoms. When the patient does experience symptoms, or symptoms endure, a more strict approach can be used (Figure 11).

Future perspectives

Rate control has settled as an appropriate treatment strategy, and a more lenient approach can now also be implicated in patients without severe AF related symptoms. Despite the results of AFFIRM and RACE, rhythm control remains an important treatment strategy in patients with AF. The last decades more and new techniques have been developed to improve the efficacy of rhythm control. The current cornerstone of rhythm control is pulmonary vein isolation (PVI). During the AFFIRM and RACE trial PVI was not yet mainstream therapy. It is possible that with superior rhythm control strategies in terms of maintenance of sinus rhythm, rhythm control will improve outcome. Currently the Catheter ablation versus anti arrhythmic drugs therapy for atrial fibrillation trial (CABANA, ClinicalTrials.gov Identifier NCT00911508) and the Early treatment of Atrial fibrillation for stroke Prevention Trial (EAST, ClinicalTrials.gov Identifier NCT01288352) are investigating the effect of PVI on cardiovascular morbidity and mortality. The primary endpoint in the CABANA is all-cause mortality. In the EAST the primary outcome is a composite of cardiovascular death, stroke, hospitalization for worsening heart failure or due to acute coronary syndrome. Rhythm control may also become more effective when upstream therapy is applied. Currently the RACE 3 (ClinicalTrials.gov Identifier NCT00877643) is

Table 6. Studies on new drugs preventing stroke or systemic embolism in AF

Study	Medication used and outcome		
RELY[130]	Dabigatran		Warfarin*
	110 mg b.i.d.	150 mg b.i.d.	
Stroke or systemic embolism (% per year)	1.53	1.11	1.69
Bleeding (% per year)	2.71	3.11	3.36
ROCKET AF[131]	Rivaroxaban 20 mg once daily		Warfarin*
Stroke or systemic embolism (% per year)	1.7		2.2
Bleeding (% per year)	3.6		3.4
ARISTOTLE[132]	Apixaban 5 mg twice daily		Warfarin*
Stroke or systemic embolism (% per year)	1.27		1.60
Bleeding (% per year)	2.13		3.09

b.i.d. - bis in die, twice a day
* Dose adjusted

investigating the effect of a combination of upstream therapies including physical exercise compared to conventional rhythm control on maintenance of sinus rhythm in patients with early AF.

Besides more effective means to maintain sinus rhythm, early detection of AF may also improve outcome. Since some patients present with a stroke as a first symptom of AF, early detection of AF may reduce cardiovascular morbidity and mortality.

Reviewing the results of the RACE II, it is striking that 28 out of 81 primary endpoints were major bleedings. Thus despite the anticoagulation clinics in the Netherlands, bleedings remain a major issue when instituting patients on oral anticoagulation. Several studies on the risk of stroke in AF, with the risk of bleeding as safety outcome, have been published (Table 6). The RELY investigated whether dabigatran (a direct thrombin inhibitor) was as effective as warfarin in preventing stroke or systemic embolism.[130] The primary safety outcome was major bleeding. Patients were eligible if they had AF and a risk factor for stroke. In total, 18,113 patients were randomized to either 110 mg dabigatran, 150 mg dabigatran, both twice daily, or warfarin. In Table 6 the results of the RELY are displayed. The 110 mg dose of dabigatran was non-inferior as compared to warfarin in preventing stroke or systemic embolism. The 150 mg dose dabigatran was superior as compared to warfarin in preventing stroke or systemic embolism. The risk of bleeding was lower with 110 mg dabigatran, as compared to warfarin. There was no difference in bleeding risk between 150 mg dabigatran and warfarin. The ROCKET AF investigated the efficacy and safety of preventing stroke and systemic embolism with rivaroxaban (a direct factor Xa inhibitor) as compared with warfarin.[131] The primary safety outcome was a composite of major and non-major clinically relevant bleeding events. Patients were eligible if they had AF and a $CHADS_2$ score of 2 or more. In total 14,264 patients were included in the trial. There was no difference in stroke or systemic embolism between

rivaroxaban and warfarin. There was also no difference in bleeding risk (Table 6). However, the patients randomized to rivaroxaban suffered less intracranial and fatal bleedings. The ARISTOTLE investigated the efficacy and safety of preventing stroke and systemic embolism with apixaban (a direct factor Xa inhibitor) as compared to warfarin.[132] The primary safety outcome was major bleeding. In total 18,201 patients were included in the trial. The rate of stroke and systemic embolism was lower in the apixaban group, as compared to warfarin. The risk of bleeding was also reduced in the apixaban group (Table 6). Furthermore, all-cause mortality was lower in the apixaban group. The RELY, ROCKET AF, and ARISTOTLE illustrate that there is still a lot to gain in the prevention of thromboembolic complications and the risk of bleeding due to anticoagulation in treatment of AF.

Since our current rate control drugs are ineffective in controlling the heart rate and subsequently improving outcome, rhythm control strategies and anticoagulation should be optimized and new studies on rate control in patients with permanent AF may bring us new drugs or strategies to improve outcome.

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Summary

In Europe more than 6 million patients have atrial fibrillation currently. It is expected that this number will double in the next 30 – 50 years. Atrial fibrillation is not a benign disease. The risk of death, stroke and heart failure is increased, in addition exercise capacity and quality of life are reduced. Despite efforts to maintain a normal rhythm, atrial fibrillation is a progressive arrhythmia; the arrhythmia is present occasionally at first but will be present continuously in the end. This means that atrial fibrillation is continuously present in a lot of patients. The treatment of this specific patient group is not evidence based. An evidence based treatment strategy is indispensable.

Atrial fibrillation has been known for a long time. Treatment consisted of maintenance of the normal rhythm with quinidine and control of the ventricular rate with digoxin. In 1960 the electrical cardioversion was introduced. Atrial fibrillation remained a progressive arrhythmia despite this new method because after successful restoration of sinus rhythm AF easily relapsed. It was not until the beginning of this decade that it became apparent that it was not the rhythm that mattered, i.e. there was no difference in outcome between rate (treatment aimed at heart rate reduction) and rhythm control (treatment aimed at maintenance of normal rhythm). However, different definitions of adequate rate control were used in the rate versus rhythm control studies. The guidelines advocated a strict rate control strategy, but this was based on small studies which did not investigate prognosis. Thus, an evidence based rate control strategy was lacking. Studies which investigated different rate control strategies showed no difference in outcome between patients with a high and low heart rate. However, these were all retrospective analysis.

Quality of life and heart rate are also assumed to be related. A higher heart rate could cause more or more severe symptoms than a lower heart rate. However, instituting a stricter rate control strategy requires more negative dromotropic drugs. Prospective data on quality of life and different rate control studies were also lacking.

Aim of this thesis was to investigate different rate control strategies in patients with atrial fibrillation. In **chapter 1** the general introduction and background is discussed, as is summarized above.

In **chapter 2** we performed a retrospective analysis on prognosis in patients with permanent AF with a low and high heart rate. The study cohort consisted of all patients randomized to rate control in the RACE study. Patients were divided according to the mean heart rate during follow-up. Low heart rate was defined as a mean heart rate below 80 beats per minute, high heart rate was defined as a mean heart rate equal to or above 80 beats per minute. We observed no difference in outcome between a low and high heart rate. In addition, there was no difference in quality of life or left ventricular function between a low and high mean heart rate.

The abovementioned results are consistent with previous studies on heart rate and prognosis, but all these studies were retrospective. Therefore, a randomized clinical trial was performed evaluating lenient and strict rate control in terms of cardiovascular morbidity and mortality, i.e. the Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II (RACE II) study. The hypothesis was that there was no difference in

outcome between lenient and strict rate control. The results of the RACE II are presented in **chapter 3**. In RACE II more than 600 patients were randomized to lenient or strict rate control. The primary outcome was a composite of cardiovascular death, hospitalization for heart failure, stroke, systemic embolism, major bleeding, or arrhythmic events, including syncope, sustained ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs, and pacemaker or cardioverter-defibrillator implantation. Heart rate was lowered with beta-blockers, non-dihydropyridine calcium-channel blockers, and digoxin, alone or in combination. After the dose-adjustment phase there was a significant difference in heart rate between the two groups. This difference remained present during the study. After a follow-up of 3 years there was no difference in primary outcome between lenient and strict rate control. This showed that lenient rate control was non-inferior to strict rate control, which confirmed our hypothesis.

Previous studies on rate control in atrial fibrillation have shown that strict rate control is difficult to achieve. We also observed this in RACE II, 67% of patients randomized to strict rate control achieved the strict rate control criteria, as compared to 97% of patients randomized to lenient rate control. This large difference could have influenced the outcome of RACE II, in favor of lenient rate control. Therefore we performed an additional analysis investigating outcome in patients with failed strict, adequate strict and lenient rate control. The results of this study are presented in **chapter 4**. We observed no difference in the primary outcome, as described above, between failed strict, successful strict and lenient rate control. This showed that failure of strict rate control did not influence the results of RACE II. This is another clue that lenient rate control can now be adopted as frontline therapy in patients with permanent atrial fibrillation.

Quality of life is another important outcome parameter in treatment of patients with permanent atrial fibrillation. Therefore we performed a predefined analysis on difference in quality of life between lenient and strict rate control. The hypothesis was that there would be no difference in quality of life between lenient and strict rate control. Quality of life was assessed with the SF-36, MFI-20 and AF-severity scale. At the end of the study there was no difference in quality of life measured with the SF-36, MFI-20 an AF-severity scale between lenient and strict rate control. In addition, heart rate did not influence quality of life. The results of this study are presented in **chapter 5**. This again showed that lenient rate control is treatment of choice in patients with permanent atrial fibrillation.

The ideal outcome parameter in a study on prognosis is mortality. However, this would require a very large patient cohort due to the good prognosis in patients with atrial fibrillation. Therefore a composite outcome was used in RACE II. Cardiovascular hospitalization is an alternative outcome parameter which is associated with mortality. To further investigate difference between lenient and strict rate control we performed an additional analysis on cardiovascular hospitalization and mortality. These results are presented in **chapter 6**. We observed no difference in cardiovascular hospitalization and mortality between lenient and strict rate control. It is, however, striking that many patients were hospitalized during the study, showing the vulnerability of patients with

permanent atrial fibrillation.

Finally, in **chapter 7** we discuss the general clinical and therapeutical implications of different rate control strategies with respect to the results presented in this thesis. Treatment on atrial fibrillation is simplified due to the results of RACE II. Lenient rate control is easy to achieve, requires fewer drugs, outpatient department visits and additional examinations. However, patients with atrial fibrillation are fragile and the risk of complications due to atrial fibrillation remains.

Samenvatting

Op dit moment hebben meer dan 6 miljoen mensen in Europa boezemfibrilleren en de verwachting is dat dit aantal zich de komende 30 tot 50 jaar zal verdubbelen, mede door de vergrijzing. Boezemfibrilleren is geen goedaardige aandoening. Er bestaat een verhoogde kans op overlijden, hersenberoerte, hartfalen, een afgenomen inspanningstolerantie en een afgenomen kwaliteit van leven. Ondanks pogingen het normale ritme te herstellen, is het een progressieve ritmestoornis. Dit betekent dat de ritmestoornis aanvankelijk af en toe aanwezig is, en uiteindelijk continu. Er zijn veel patiënten bij wie de ritmestoornis continu aanwezig is. Een evidence based behandelstrategie ontbreekt op dit moment bij deze patiënten en is vanwege het grote aantal patiënten van groot belang.

Boezemfibrilleren is al zeer lang een bekende ritmestoornis. Vroeger werd de hartfrequentie verlaagd met digoxine of er werd geprobeerd het normale ritme terug te krijgen met quinidine. In de jaren 60 van de vorige eeuw is de electrische cardioversie geïntroduceerd. Ondanks deze nieuwe methode bleef boezemfibrilleren een progressieve ritmestoornis. Er waren, en zijn, twee behandelstrategiën voor boezemfibrilleren: ritme controle en frequentie controle. Een ritme controle strategie is gedefiniëerd als een behandeling gericht op het behoud van normaal ritme (sinusritme). Een frequentie controle strategie is gedefiniëerd als een behandeling gericht op verlaging van de hartfrequentie tijdens de ritmestoornis.

Het is nu 10 jaar geleden dat duidelijk is geworden dat er geen verschil in prognose is tussen een behandeling volgens een ritme controle of een behandeling volgens een frequentie controle strategie. De studies die dit hebben laten zien gebruikten verschillende definities voor goede hartfrequentie controle. De richtlijnen op dat moment adviseerden een strenge frequentie controle. Dit advies was echter gebaseerd op kleine studies die niet naar de prognose van de patiënt keken. Er was daarmee geen goed bewijs hoe patiënten behandeld moesten worden volgens een frequentie controle strategie. Er werd verondersteld dat bij boezemfibrilleren hartfrequentie en prognose aan elkaar gerelateerd zijn. Studies die verricht zijn naar frequentie controle, lieten geen verschil in prognose zien tussen patiënten met een hoge of lage hartfrequentie. Hierbij moet worden aangemerkt dat dit retrospectieve studies zijn.
Ook is verondersteld dat hartfrequentie en kwaliteit van leven aan elkaar gerelateerd zijn. Een hogere hartfrequentie zou meer en ernstigere klachten kunnen veroorzaken. Maar, een strenge behandel strategie behoeft meer medicatie, met mogelijk meer bijwerkingen. Er zijn geen prospectieve gegevens over de relatie tussen kwaliteit van leven en hartfrequentie, noch ook tussen kwaliteit van leven en verschillende frequentie controle strategieën.

Het doel van dit proefschrift is om verschillende frequentie controle strategieën voor de behandeling van boezemfibrilleren met elkaar te vergelijken. In **hoofdstuk 1** zijn de algemene introductie en achtergrond van dit proefschrift behandeld, zoals hierboven is samengevat.

Vervolgens hebben we in een retrospectieve studie gekeken naar de prognose bij patiënten met een hoge en lage hartfrequentie. Deze resultaten zijn gepresenteerd in **hoofdstuk 2**. De patiëntengroep bestond uit patiënten geincludeerd in de RACE

studie die gerandomiseerd (willekeurig ingedeeld) waren naar frequentie controle. De patiënten zijn daarna ingedeeld op basis van de gemiddelde hartfrequentie tijdens de studie. Een hartfrequentie onder de 80 slagen per minuut is in deze studie gedefinieerd als een lage hartfrequentie en een frequentie gelijk aan, of hoger dan, 80 slagen per minuut als een hoge hartfrequentie. Hierbij is naar voren gekomen dat er geen verschil was in prognose tussen de patiënten met een lage en een hoge hartfrequentie. Daarnaast is er ook geen verschil in kwaliteit van leven of verslechtering van de linker ventrikelfunctie bij patiënten met een hoge hartfrequentie.

Bovengenoemde uitkomsten komen overeen met de resultaten van eerdere onderzoeken naar hartfrequentie controle tijdens boezemfibrilleren. Hierbij moet worden aangemerkt dat evenals in ons onderzoek eerdere studies naar frequentie controle bij boezemfibrilleren retrospectief waren. Om die reden hebben we een prospectief, dubbel blind, gerandomiseerde studie verricht naar het effect van frequentie controle op de prognose bij patiënten met permanent boezemfibrilleren. In **hoofdstuk 3** zijn de resultaten van 'The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II study (RACE II)' gerapporteerd. In de RACE II hebben we meer dan 600 patiënten gerandomiseerd naar een strenge frequentie controle of gematigde frequentie controle. Een strenge frequentie controle is gedefinieerd als een rust-frequentie onder de 80 slagen per minuut én tijdens gematigde inspanning onder de 110 slagen per minuut. Een gematigde frequentie controle is gedefinieerd als een rust-frequentie onder de 110 slagen per minuut. De hypothese was dat gematigde frequentie controle niet slechter zou zijn dan strenge frequentie controle. Het primaire eindpunt was een combinatie van cardiovasculair overlijden, opname voor hartfalen, beroerte, bloedingen, pacemaker of interne defibrillator implantatie, levensbedreigende complicaties van de frequentie controle medicatie, syncope of levensbedreigende kamer ritmestoornissen. De hartfrequentie werd verlaagd met beta-blockers, calcium antagonisten of digoxine. Na de dosis-titratie fase was er een significant verschil in hartfrequentie tussen de beide groepen. Tijdens de studie bleef er een significant verschil in hartfrequentie bestaan. Na een studieduur van 3 jaar was er geen verschil in het optreden van het primaire eindpunt tussen de gematigde en strenge frequentie controle groep. Dit betekent dat de gematigde frequentie controle strategie niet slechter is dan de strenge frequentie controle strategie. Hiermee is onze hypothese bevestigd, en is een gematigde frequentie controle de eerste keus behandelstrategie bij patiënten met permanent boezemfibrilleren.

Eerdere studies naar frequentie controle bij permanent boezemfibrilleren lieten zien dat het moeilijk is om patiënten in te stellen op een strenge frequentie controle. Dit probleem hebben we ook gezien in de RACE II. In de strenge frequentie controle strategie van de RACE II heeft 67% van de patiënten de hartfrequentie criteria gehaald tegenover 98% van de patiënten in de gematigde frequentie controle groep. Dit grote verschil zou, in het voordeel van de gematigde behandel strategie, de uitkomsten van de RACE II beïnvloed kunnen hebben. We hebben daarom een aanvullende analyse verricht naar het verschil in prognose tussen patiënten met succesvolle strenge frequentie controle, niet succesvolle strenge

frequentie controle en gematigde frequentie controle. De resultaten van deze studie zijn in **hoofdstuk 4** gepresenteerd. Deze studie laat zien dat er geen verschil is in het primaire eindpunt, zoals hierboven beschreven, tussen succesvolle en niet succesvolle strenge frequentie controle en gematigde frequentie controle. Dit betekent dat het door patiënten niet behalen van de strenge frequentie controle geen invloed heeft gehad op de uitkomsten van de RACE II. Deze bevinding wijst er wederom op dat gematigde frequentie controle de eerste keus behandelstrategie is bij patiënten met permanent boezemfibrilleren.

Naast de prognose van de patiënt is kwaliteit van leven een belangrijk aspect bij de behandeling van boezemfibrilleren. Daarom hebben we in de RACE II een analyse verricht naar het verschil in kwaliteit van leven tussen de patiënten met gematigde en strenge frequentie controle strategie. De hypothese was dat er geen verschil in kwaliteit van leven zou zijn tussen deze twee groepen. Kwaliteit van leven is gemeten met 3 vragenlijsten, de SF-36, MFI-20 en AF-severity scale. Dit zijn vragenlijsten naar respectievelijk algemene gezondheid, vermoeidheid en klachten gerelateerd aan boezemfibrilleren. Aan het einde van de studie was er geen verschil in kwaliteit van leven tussen de twee behandelstrategieën. Daarnaast had ook hartfrequentie geen invloed op verschil in kwaliteit van leven. Deze resultaten zijn gepresenteerd in **hoofdstuk 5** en laten wederom zien dat gematigde frequentie controle de eerste keus behandelstrategie is bij patiënten met permanent boezemfibrilleren.

Een studie die wetenschappelijk bewijs moet leveren heeft in het ideale geval overlijden als primair eindpunt. Patiënten met boezemfibrilleren hebben een dermate goede prognose dat er zeer veel patiënten nodig zijn om zo'n studie statistisch verantwoord uit te voeren. In de RACE II is daarom gebruik gemaakt van een gecombineerd eindpunt. Opname vanwege cardiovasculaire redenen is een alternatief eindpunt dat gerelateerd is aan overlijden. Om toch een uitspraak te kunnen doen over overlijden hebben we in de RACE II een aanvullende analyse verricht naar overlijden en opname vanwege cardiovasculaire redenen. Deze studie is gepresenteerd in **hoofdstuk 6**. In deze studie zien we dat er geen verschil is tussen de gematigde en strenge frequentie controle groep in overlijden en opname vanwege cardiovasculaire redenen. Het is wel opvallend dat veel van de patiënten tijdens de studieduur zijn opgenomen. Dit laat zien dat patiënten met boezemfibrilleren kwetsbaar zijn.

Tot slot behandelen we in **hoofdstuk 7** de algemene klinische en therapeutische implicaties van rate control strategieën in boezemfibrilleren waarbij we verwijzen naar de bevindingen van dit proefschrift. In de toekomst denken we dat de behandeling van boezemfibrilleren mede door de resultaten van dit proefschrift vereenvoudigd kan worden. Gematigde frequentie controle is eenvoudiger te behalen, met minder medicatie, minder ziekenhuis bezoeken en minder aanvullend onderzoek. Hierbij moet wel aangetekend worden dat patiënten met boezemfibrilleren kwetsbaar zijn en het risico op complicaties van de ritmestoornis of de behandeling blijft bestaan.

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De basis van mijn proefschrift is gelegd toen de RACE II is opgezet. Nadat de RACE studie was afgerond was de RACE II een logisch vervolg, maar de RACE II is wel de enige studie in zijn soort. Voor het bedenken, ontwerpen, opzetten en uitvoeren van deze studie ben ik de steeringcommissie ontzettend dankbaar. Beste Harry, Jan, Hans, Dirk Jan, Maarten, Ype, Marco, Hans, Jan-Hein, Otto en Isabelle, dank voor jullie vooruitstrevende ideeën en werk.

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